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Authors

Mielke, Michelle M
Aggarwal, Neelum T
Vila-Castelar, Clara
et al.

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PERSPECTIVE

Consideration of sex and gender in Alzheimer's disease and related disorders from a global perspective

Michelle M. Mielke^{1,2} | Neelum T. Aggarwal^{3,4} | Clara Vila-Castelar⁵ |
Puja Agarwal^{4,6} | Eider M. Arenaza-Urquijo^{7,8,9} | Benjamin Brett¹⁰ |
Anna Brugulat-Serrat^{7,8,9,11} | Lyndsey E. DuBose¹² | Willem S. Eikelboom¹³ |
Jason Flatt¹⁴ | Nancy S. Foldi^{15,16} | Sanne Franzen¹³ | Paola Gilsanz¹⁷ | Wei Li¹⁸ |
Alison J. McManus¹⁹ | Debora Melo van Lent^{20,21,22} | Sadaf Arefi Milani²³ |
C. Elizabeth Shaaban²⁴ | Shana D. Stites²⁵ | Erin Sundermann²⁶ |
Vidyani Suryadevara²⁷ | Jean-Francoise Trani²⁸ | Arlener D. Turner²⁹ |
Jet M. J. Vonk^{30,31} | Yakeel T. Quiroz^{5,32} | Ganesh M. Babulal^{33,34,35} | for the Diversity
and Disparity Professional Interest Area Sex and Gender Special Interest Group

¹Division of Epidemiology, Department of Quantitative Health Sciences, Mayo Clinic, Rochester, Minnesota, USA

²Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA

³Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois, USA

⁴Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, Illinois, USA

⁵Department of Psychiatry, Harvard Medical School, Massachusetts General Hospital, Massachusetts, Boston, USA

⁶Department of Internal Medicine, Rush University Medical Center, Chicago, Illinois, USA

⁷Barcelonaβeta Brain Research Center (BBRC), Pasqual Maragall Foundation, Barcelona, Spain

⁸IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain

⁹CIBER Fragilidad y Envejecimiento Saludable (CIBERFES), Madrid, Spain

¹⁰Department of Neurosurgery, Medical College of Wisconsin, Wisconsin, Milwaukee, USA

¹¹Atlantic Fellow for Equity in Brain Health, The University of California San Francisco, San Francisco, California, USA

¹²Department of Medicine, Division of Geriatrics, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA

¹³Department of Neurology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

¹⁴Social and Behavioral Health Program, School of Public Health, University of Nevada, Las Vegas, Las Vegas, Nevada, USA

¹⁵Department of Psychology, Queens College and The Graduate Center, City University of New York, New York, USA

¹⁶Department of Psychiatry, New York University Long Island School of Medicine, New York, USA

¹⁷Kaiser Permanente Division of Research, Oakland, California, USA

¹⁸Department of Clinical and Diagnostic Sciences, University of Alabama at Birmingham, Birmingham, Alabama, USA

¹⁹Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts, USA

²⁰UT Health San Antonio, Glenn Biggs Institute for Alzheimer's and Neurodegenerative diseases, San Antonio, Texas, USA

²¹Framingham Heart Study, Framingham, Massachusetts, USA

²²Department of Neurology, Boston University School of Medicine, Boston, Massachusetts, USA

²³Division of Geriatrics & Palliative Medicine, Department of Internal Medicine, University of Texas Medical Branch, Galveston, Texas, USA

²⁴Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

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²⁵Department of Psychiatry, Perlmutter School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

²⁶Department of Psychiatry, University of California, San Diego, California, USA

²⁷Department of Orthopedic Surgery, Rush University Medical Center, Chicago, Illinois, USA

²⁸Department of Public Health, Washington University in St. Louis, St. Louis, Missouri, USA

²⁹Department of Psychiatry & Behavioral Sciences, University of Miami Miller School of Medicine, Miami, Florida, USA

³⁰Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University, New York, New York, USA

³¹Julius Center for Health Sciences and Primary Care, Department of Epidemiology, University Medical Center Utrecht and Utrecht University, Utrecht, The Netherlands

³²Grupo de Neurociencias de Antioquia of Universidad de Antioquia, Medellin, Columbia, USA

³³Department of Neurology, Washington University in St. Louis, St. Louis, Mississippi, USA

³⁴Department of Clinical Research and Leadership, The George Washington University School of Medicine and Health Sciences, Washington, DC, USA

³⁵Department of Psychology, Faculty of Humanities, University of Johannesburg, Johannesburg, South Africa

Correspondence

Michelle M. Mielke, Department of Quantitative Health Sciences, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.
Email: Mielke.Michelle@mayo.edu

Michelle M. Mielke, Neelum T. Aggarwal, and Clara Vila-Castelar denotes co-first authors.

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Abstract

Sex or gender differences in the risk of Alzheimer's disease and related dementias (ADRD) differ by world region, suggesting that there are potentially modifiable risk factors for intervention. However, few epidemiological or clinical ADRD studies examine sex differences; even fewer evaluate gender in the context of ADRD risk. The goals of this perspective are to: (1) provide definitions of gender, biologic sex, and sexual orientation, and the limitations of examining these as binary variables; (2) provide an overview of what is known with regard to sex and gender differences in the risk, prevention, and diagnosis of ADRD; and (3) discuss these sex and gender differences from a global, worldwide perspective. Identifying drivers of sex and gender differences in ADRD throughout the world is a first step in developing interventions unique to each geographical and sociocultural area to reduce these inequities and to ultimately reduce global ADRD risk.

KEYWORDS

Alzheimer's, ethnicity, gender, global health, risk factors, sex, sociocultural factors

Highlights

- The burden of dementia is unevenly distributed geographically and by sex and gender.
- Scientific advances in genetics and biomarkers challenge beliefs that sex is binary.
- Discrimination against women and sex and gender minority (SGM) populations contributes to cognitive decline.
- Sociocultural factors lead to gender inequities in Alzheimer's disease and related dementias (ADRD) worldwide.

RESEARCH IN CONTEXT

- 1. Systematic review:** The authors reviewed the literature of sex and gender differences on the risk, incidence, diagnosis, and clinical presentation of Alzheimer's disease and related dementias (ADRD) worldwide using traditional sources (eg, PubMed). Relevant citations are cited appropriately.
- 2. Interpretation:** The manuscript emphasizes the need to expand the definitions of gender and sex, consider sociocultural factors that lead to gender inequities in ADRD, and examine gender and sex differences in AD incidence, risk factors, and clinical presentations worldwide.
- 3. Future directions:** Experts from the Sex and Gender Differences Special Interest Group, part of the Diversity and Disparities Professional Interest Area of the International Society to Advance Alzheimer's Disease and Treatment (ISTAART), outline critical gaps in knowledge and identify the next steps to improve healthy cognitive aging worldwide. Advancing and translating our understanding of drivers of sex and gender differences unique to each geographical and sociocultural area is a first step in developing interventions to reduce global ADRD risk.

1 | INTRODUCTION

Rising life expectancy around the world suggests that the prevalence of Alzheimer's disease and related dementias (ADRD) will increase sharply to more than 140 million in 2050.¹ Notably, expected increases in life expectancy are not evenly distributed around the world. Countries that already have longer life expectancies (ie, high-income countries [HICs]) will not have as dramatic of an increase in ADRD compared to low-middle income countries (LMICs), which are facing rapid increases in lifespan.² The increasing burden of dementia among LMICs underscores the need for ADRD researchers to take a global perspective to identify potential risk and protective factors to improve healthy brain aging for all.

The burden of dementia is not only unevenly distributed geographically, but also by sex and gender. Although many studies of North and South American cohorts have not observed a sex difference in the incidence of ADRD,³⁻¹¹ several studies conducted in Europe¹²⁻¹⁶ and Asia^{17,18} suggest a higher incidence in women, especially after the age of 80 years. In contrast, the United Kingdom Cognitive Function and Ageing Study initially reported a higher incidence among men between 1989 and 1994, but no sex difference in incidence between 2008 and 2011.¹⁹ Few studies from LMICs have reported sex and gender differences in the incidence of ADRD, with mixed results that appear to differ by area of the world.

Individual countries or regions have unique sociocultural and sociopolitical differences, as well as historical experiences that vary

by sex and gender, and may differentially impact risk of ADRD.^{20,21} In addition, access to health care or education, opportunities to participate in research studies, and gender roles (eg, working outside the home, childcare responsibilities) are associated with risk of ADRD and differ by country.^{22,23} Although previous perspectives have either highlighted the need to study ethnic and racial disparities or sex and gender differences in ADRD risk, the examination of sex and gender differences from a global perspective is needed. Identifying drivers of sex and gender differences in ADRD throughout the world is a first step in developing interventions unique to each geographical and sociocultural area to reduce these inequities and to ultimately reduce ADRD risk. The goals of this perspective are to: (1) provide definitions of gender, biologic sex, and sexual orientation and the limitations of examining these as binary variables; (2) provide an overview of what is known with regard to sex and gender differences in the risk, prevention, and diagnosis of ADRD; and (3) discuss these sex and gender differences from a global, worldwide perspective. Members of the Sex and Gender Differences Special Interest Group, part of the Diversity and Disparities Professional Interest Area of International Society to Advance Alzheimer's Disease and Treatment (ISTAART), outline critical gaps in knowledge before interventions can be conducted to improve healthy cognitive aging and reduce ADRD risk worldwide.

2 | THE NEED TO EXPAND DEFINITIONS OF GENDER AND SEX (TABLE 1)**2.1 | Gender, biological sex, and sexual orientation**

Many articles have used the terms "sex" and "gender" interchangeably, including their prominent binary labels of male/female and man/woman, respectively.²⁴ However, sex and gender are distinct concepts and individuals are characterized by *both*. Sex is a biological variable defined by characteristics encoded in DNA, such as reproductive

TABLE 1 Gaps in knowledge regarding gender, biological sex, and sexual orientation in Alzheimer's disease and related dementias (ADRD)

Gaps in Knowledge and Translational Outlook

- Better understanding of world-wide differences in the influence of gender as a social construct on ADRD and other health outcomes and how these differences vary by age, migration status, socioeconomic status, and race/ethnicity.
- Need to move beyond defining sex and gender as binary variables. The development of additional scales and rephrasing of research questionnaires on sex/gender is warranted.
- Efforts are needed to recruit and enroll sexual and gender minority populations into research and to identify factors that contribute to dementia risk in these populations across the world.
- Additional focus on the interaction between chromosomes, hormones, and sociocultural factors on risk of ADRD is needed.

Abbreviation: ADRD, Alzheimer's disease and related dementias.

organs and other physiological and functional characteristics.²⁵ Gender refers to social, cultural, and psychological traits linked to individuals through social context. Both sex, gender, and their interactions influence health and disease.²⁵

Historically, sex has been considered as a binary construct (male or female) and defined by differences in chromosomes (XX vs XY), sex organs, endogenous hormones, and/or other characteristics encoded in DNA.^{25,26} However, scientific advances in genetics and biomarkers challenge beliefs that sex is binary.²⁷ Growing evidence demonstrates the existence of nonbinary populations, intersex populations,²⁷ and biologic correlates of gender identity.²⁸ Moreover, gender identity and sexual orientation occur on a continuum. Sexual orientation characterized as asexual, bisexual, gay or lesbian, heterosexual, queer, or another identify is often defined by the sex of an individual assigned at birth and those to whom the individual is sexually, emotionally, and romantically attracted.^{29–33} The effects of these factors may differ across other social and demographic variables such as by race and ethnicity, age, socioeconomic status (SES), culture, or migration status.^{34,35} Reinforcement of binary ideas of sex and gender have historically fortified inequities for those who identify outside societal norms, reified stereotypes of masculinity and femininity,³⁶ and contributed to economic and social disparities.³⁷ This includes limiting access to effective and appropriate health care and participation in clinical research.^{38–40}

Sex, gender, sexual orientation, and their interactions demand attention in ADRD. Two challenges include the over-reliance on self-reported sex and gender, which often assesses only binary categories and assumes homogeneity within categories,^{41,42} and the underrepresentation of sex and gender minority (SGM) populations in clinical research.³⁸ Emergent research shows that sex, sexual orientation, and gender identity can impact dementia outcomes through the process of social marginalization.²⁸

3 | SOCIOCULTURAL ASPECTS THAT LEAD TO GENDER INEQUITIES (TABLE 2)

3.1 | Education

It is well established that low education increases the risk of dementia for women and men worldwide.^{43,44} Some studies conducted in HICs,^{14,45} although not all,⁴⁶ report a similar risk for women and men with low education, which is defined based on geographic area. However, more women are affected by this risk factor because women have historically endured limited educational opportunities in both HICs and LMICs.^{47,48} In addition to the direct effects of education on ADRD risk that some studies have reported, the historically lower educational attainment in women may increase ADRD risk indirectly through high levels of distress and mental health symptoms.⁴⁹

Obstacles in obtaining education for women residing in LMICs, or women in HICs who immigrated from LMICs, begin in childhood. According to the United Nations Educational, Scientific and Cultural

TABLE 2 Gaps in knowledge regarding sociocultural aspects that lead to gender disparities

Gaps in Knowledge

- Women have historically endured limited educational opportunities in both high- and low-middle-income countries. There is a need for better understanding of the intersection between sociocultural gender roles and risk of ADRD, especially in low-middle-income countries.
- Access to education for women in high-income countries has increased and it is important to understand the implications of this trend on future risk of ADRD.
- Additional examination of if, and how, employment and occupational characteristics differ by gender in diverse cultural settings worldwide, and whether the trends of increasing women in the workforce in some countries affect the risk of ADRD.
- Examination of gender differences in social experiences, including discrimination of women across different geographical regions and social strata or caste, with the development of late-life cognitive decline and dementia.
- Access to care, risk factors, and dementia diagnosis in sexual and gender minority populations can differ across the world based on the greater acceptance or discrimination of these populations by specific cultures. Better understanding of the impact of these barriers on ADRD, and how to overcome them, is needed.

Abbreviation: ADRD, Alzheimer's disease and related dementias.

Organization (UNESCO), 132 million girls are out of school worldwide. In countries where girls enter primary school, only a small portion matriculate, and far fewer complete secondary school. In conflict settings, girls are more than twice as likely to be out of school.^{50–52} Traditional obstacles like poverty, armed conflict/violence, cultural traditions (eg, child marriage), and deprived infrastructures for education (eg, crumbling schools) increase the likelihood of educational exclusion for girls.⁵³ The coronavirus disease 2019 (COVID-19) pandemic has further exacerbated these societal and life course inequities with prolonged school closures, household work responsibilities, caregiving, and more violence against girls and women.

Studies show that gender attitudes and stereotypes considerably influence women's participation in socioeconomic activities and explain a persistent gap in access to school and educational achievements.^{53–55} Patriarchal norms may determine gender roles through the socialization processes promoted at schools. In particular, the education curriculum itself may perpetuate traditional gender bias and prevent the questioning of gender inequality in educational systems.⁵⁶ Hidden curricula promote values and behaviors that are not challenged by students.^{57,58} In some LMICs, a woman's role is traditionally defined in the private sphere as in homemaking, caregiving, and reproduction; education might reinforce these traditional norms for gender roles and fail to equip critical thinking to question these roles.⁵⁹ Working toward reducing the barriers for education for women across the globe will mitigate the risk for dementia attributed by low education.

3.2 | Occupation

Occupational opportunities have been historically patterned by gender social norms, with more men typically residing in the workforce compared to women.⁶⁰ In addition, occupations have historically been segregated by gender, with women being less likely to be in professional or managerial positions and more likely to fill roles considered unpaid labor, which includes caregiver.⁶¹ A meta-analysis of nine prospective studies found that professional or managerial positions were associated with a 22% reduction in cognitive decline and 44% reduction in mild cognitive impairment (MCI).⁶² However, only a few studies, all among HICs, have examined the role of gender and occupation jointly when considering dementia risk, and the results have been inconclusive. A prospective study of almost 3000 French men and women found that compared to professional/managerial positions, being a craftsman or shopkeeper was associated with over a 50% reduced risk of AD among women, but a doubling of AD risk among men.⁶³ In contrast, a prospective study of over 900 Swedish individuals found that occupations related to the production of goods were associated with a doubling of dementia risk among women compared to non-manual labor, but not among men.⁶⁴ Low-control work has been associated with an increased risk of dementia among women,⁶⁵ and high-control work with a lower risk of dementia among men.⁶⁶ However, another study reported few gender differences in the relationships between work control and ADRD.⁶⁷ Potential reasons for the discrepancies may be the use of Job Exposure Matrices, which has limited generalizability across countries,⁶⁸ and the lack of consideration of apolipoprotein E (APOE) genotype, which may interact with gender and work control when examining risk of ADRD.⁶⁶

3.3 | Discrimination

Discrimination against women and SGM populations contributes to gender differences in late-life cognitive health. The discrimination can be subtle or explicit, conscious or unconscious, and vary by racial and ethnic minority groups and area of the world. Gender is a major social and structural determinant of health and influences access to resources that permeate all areas of society. Gender discrimination in the workplace (ie, women receiving unequal pay and harassment) can lead to excess stress and reduced income that could ultimately result in greater poverty and less access to medical care.⁶⁹ Little research has examined the effects of sex- and gender-based discrimination on risk, diagnosis, and treatment of ADRD and whether these effects vary by racial and ethnic minority groups or region of the world.

The impact of discrimination on ADRD risk varies with cultural and historical context and geography. For example, in the Longitudinal Aging Study in India,⁷⁶ educational attainment explained about 60% of the gender inequity in late-life cognitive health. However, when stratified by region (north and south) the disadvantage in cognitive function remained only for women in northern India, which was explained by an overall higher prevalence of discrimination against women in that

region.^{77,78} These findings were consistent with earlier literature that noted that women in the northern state of Haryana performed worse than men on cognitive tests⁷⁹ but no gender difference in southern India.⁸⁰ The interplay of different types of discrimination on ADRD risk can vary by region and needs to be investigated in areas across the world.

3.4 | Medical treatment and access

Medical treatment and access comprise several components that include the financial means to access care, the availability of care needed, and the patient's experience—real or anticipated—of receiving care. Stigma, fear, and discrimination can modify each of those components in ways that exacerbate barriers to care based on sex, gender, and status as a member of SGM populations. The ways in which this occurs differs across nations and parts of the world because social, cultural, and historical contexts impact factors that influence both health care delivery and the social status of individuals based on sex/gender.

In the United States, the burden of health care costs is felt disproportionately by women. More than half of American women (52%) in 2018 said they worried about not having enough money to pay for health care, compared to 40% of men.⁷⁰ Moreover, a higher proportion of women than men also cited the possibility of paying higher premiums or having to go without health insurance as a major concern.⁷⁰ The proportion of US women foregoing health care and underusing prescription medication due to costs is significantly higher than the proportion of men. In addition, women report lower levels of communication with their physicians about drug costs than White, male, and younger patients.⁷¹ These findings suggest that the high cost of care reflects a gender bias in the United States and may contribute to gender inequities in health outcomes, including ADRD.

In communities across sub-Saharan Africa, women face multiple barriers to accessing and receiving care including the availability of services, stigma, and discrimination.⁷² Married women—who are largely responsible for anchoring the family system—experience worse mental health and well-being than divorced women.⁷³ Thus, in this area, a women's social role and responsibility are barriers to self-care and health care access.

Worldwide discriminative behaviors experienced by SGM patients in both HICs and LMICs include stigma, denial, or refusal of health care; verbal or physical abuse; and inadequate provider knowledge.^{40,74} Transgender populations are less likely to have financial access to appropriate medical care.^{75,76} For example, gay men encounter negative social pressure, discrimination, and even violence when accessing medical care in sub-Saharan Africa.⁷⁷ In addition, the knowledge, beliefs, and religion of health care providers affect attitudes and behaviors toward SGM patients. Stigma and discrimination are also barriers for SGM individuals becoming health care providers,⁷⁸ which further impedes efforts to advance research and improve quality of care for these populations.

TABLE 3 Gaps in knowledge regarding sex-specific risk factors**Gaps in Knowledge**

- Sex differences and sex-specific risk factors for ADRD should be evaluated in more diverse samples.
- There are racial/ethnic differences in pregnancy and menopause. For instance, non-Hispanic Black women, on average, go through the menopause transition at an earlier age,¹¹⁵ experience a greater frequency of hot flashes,¹¹⁶ and are more likely to have hypertensive disorders of pregnancy and premenopausal bilateral oophorectomy, compared to White women. The impact of these differences in risk of ADRD are not understood.
- Little research has examined the impact of sociocultural views, which influence family size and marital roles, on risk of ADRD.
- The dose, duration, and access to hormonal contraceptives and menopausal hormone therapy differ around the world. The impact of these differences on the risk of ADRD are not known.
- Additional studies examining the effects of prostate cancer and androgen-deprivation therapy on the risk of ADRD in males is needed, especially studies that incorporate multiple races/ethnicities and regions around the world.
- The impact of low testosterone in males on risk of ADRD is still not well understood.

Abbreviation: ADRD, Alzheimer's disease and related dementias.

4 | SEX-SPECIFIC RISK FACTORS (TABLE 3)

Sex differences in risk factors or conditions fall into two categories: (1) diseases or conditions that are specific to one sex, and (2) diseases or conditions that have distinct causes, manifestations, outcomes (morbidity or mortality), or response to treatments in one sex compared with the other. Pregnancy and menopause are two female-specific conditions, whereas prostate cancer and its treatment with androgen deprivation therapy (ADT) is male-specific. It is important to understand how these sex-specific conditions are associated with an increased risk of developing cognitive dysfunction and dementia.

4.1 | Hypertensive disorders of pregnancy

Hypertensive disorders of pregnancy (HDPs), including gestational hypertension and preeclampsia, affect ≈5% to 15% of pregnancies but the prevalence differs by racial and ethnic minority groups.⁷⁹ In 2019, the highest incidence of HDPs was observed in South Asia, western sub-Saharan Africa, and eastern sub-Saharan Africa. The lowest incidence was in Australasia, Oceania, and Central Europe.⁸⁰ HDPs are associated with brain atrophy and cognitive decline detected as early as 5 to 15 years after the index pregnancy,^{81–85} and they are also associated with risk for dementia.^{86–88}

4.2 | Menopause

Early menopause, especially before the age of 40 (either spontaneous or due to bilateral oophorectomy) is associated with an increased risk of MCI, AD, and medial temporal lobe neurodegeneration.^{89–94} This risk is most pronounced among women who do not use menopausal hormone therapy (MHT) up until the age of 50. In addition, longitudinal declines in cerebral metabolism and hippocampal atrophy and increased brain amyloid beta ($A\beta$) deposition are greater over the menopause transition compared to men of the same age, independent of APOE status and cardiovascular risk factors.⁹⁵ Cognitive benefits of MHT remain controversial, but the conflicting results may be due to differences in the timing of MHT initiation in relation to menopause. Recent results indicate that the initiation of MHT shortly after the final menstrual period does not have long-term harmful or beneficial cognitive effects.^{96,97} The types, doses, duration, and availability of MHT for menopausal symptoms vary worldwide.⁹⁸ Limited access to MHT due to prescribing practices or supply shortages remains an issue in many countries.

4.3 | Androgen deprivation therapy (ADT) and testosterone

Approximately 11% of men are diagnosed with prostate cancer within their lifetime, although this varies based on regions of the world.⁹⁹ More than half of men in HICs diagnosed with prostate cancer receive ADT at some point in their treatment, which drastically lowers testosterone levels.¹⁰⁰ Some studies, but not others, suggest that ADT use may be associated with a risk of cognitive impairment and dementia.^{101–106} In addition, men experience declines in testosterone levels with age, ≈2% to 3% per year after the age of 30.¹⁰⁷ It remains unclear whether low testosterone levels are associated with a risk of dementia in men.¹⁰⁸

5 | SEX AND GENDER DIFFERENCES IN RISK FACTORS (TABLE 4)

Several studies have identified modifiable risk factors across the lifespan for ADRD, many of which were highlighted in the 2020 report of the Lancet Commission.¹⁰⁹ Notably, although the prevalence of smoking and vascular factors is decreasing in HICs, these ADRD risk factors are increasing in LMICs.¹ However, studies examining these risk factors do not uniformly examine sex or gender differences in LMICs or HICs, and only adjust for sex/gender instead. This section provides some examples of sex and gender differences in risk factors for ADRD.

5.1 | Cardiometabolic risk factors

Globally, hypertension is the leading cause of mortality and disability-adjusted life years (DALYs) and the burden is predominantly in

TABLE 4 Gaps in knowledge regarding sex and gender differences in risk factors**Gaps in Knowledge**

- Most studies adjust for sex/gender when examining risk factors for ADRD (eg, cardiometabolic, sleep, depression, diet and physical activity, traumatic brain injury, or pain), but do not examine sex differences.
- Moreover, most studies have focused on North American or European populations, especially non-Hispanic White populations. It is essential to include other ethnic groups, countries, and cultures in future studies.
- Limited research has explicitly examined sex differences in the association between midlife blood pressure, hypertension, or treatment and risk of ADRD.
- Examination of sex- and gender-related factors that contribute to sleep disorders across the lifespan and in relation to subsequent risk of ADRD, as well as sex and gender differences in sleep disorders among people living with ADRD, is needed.
- Sex and gender differences in the interaction between the biological and sociocultural factors that contribute to depression, and subsequently to ADRD, are not well understood. Furthermore, although the expression of depressive symptoms and treatment seeking varies by sex, race/ethnicity, and region of the world, the impact of the differences in expression on the risk of ADRD is not clear.
- Most research examining TBI as a risk factor for ADRD has been in the setting of sports. There is an urgent need to expand this research to other areas. For example, intimate partner violence is at epidemic proportions, with up to one of three women worldwide experiencing severe violence during their lifetime, which often results in TBI.²⁷⁷
- Additional research is needed to further quantify the prevalence of TBI, including repeat injury, in this population and to examine its relationship to ADRD.
- Examination of the role of sex and gender in the relationship between pain, pain medication, and ADRD, particularly across diverse settings.

Abbreviations: ADRD, Alzheimer's disease and related dementias; TBI, traumatic brain injury.

LMICs.¹¹⁰ Midlife blood pressure has been associated with a risk of ADRD.¹¹¹⁻¹¹⁷ Males have a higher incidence of hypertension than females until after females have transitioned through menopause.¹¹⁸ Limited research has explicitly examined the sex differences in the association between midlife blood pressure or hypertension and ADRD risk.¹¹⁹ Although some studies have shown a stronger association between blood pressure and risk of ADRD in females,^{116,120} others have found no sex difference^{121,122} or a stronger association in males.¹²² Sample characteristics, such as age ranges, may explain some of these inconsistencies. Furthermore, although the burden of hypertension is greater in LMICs, most of the research examining midlife blood pressure has been conducted in HICs. A systematic review of

dementia prevalence in Africa (six countries) found that female sex, older age, and cardiovascular disease were independently associated with an increased risk of dementia.¹²³ A cross-sectional study of Chinese older adults (≥ 60) found similar results for female sex, hypertension, and a number of other cardiovascular risk factors that increased the risk for MCI and dementia.¹²⁴ Neither the studies in Africa nor in China assessed the interaction between sex and cardiovascular factors.

Additional longitudinal research in HICs and LMICs is needed to disentangle possible sex-specific pathways linking midlife blood pressure to ADRD.¹¹⁹

Metabolic syndrome (MetS), the cluster of cardiometabolic risk factors including obesity, hypertension, impaired glucose regulation, and dyslipidemia, is a well-established risk factor for ADRD.^{125,126} The prevalence of MetS in females depends on menopausal status; changes in sex hormones with the menopause transition promote insulin resistance and a proatherogenic lipid profile, which are causal factors for impaired glucose regulation and dyslipidemia, respectively.¹²⁶ A meta-analysis showed that MetS posed a stronger risk of developing ADRD for females, as compared to males.¹²⁵ Explanations include sex differences in the distribution of central adiposity, lipid profiles, hormones, and platelet biology and biochemistry.¹²⁵ For example, findings from the Jackson Heart Study reported that females had higher abdominal subcutaneous adipose mass, whereas males had higher abdominal visceral adipose mass.¹²⁶

5.2 | Sleep

Approximately 50 to 70 million people in the United States alone report a sleep disorder.¹²⁷ Of the multiple categories of sleep disorders, sex and gender differences have been identified for insomnia, obstructive sleep apnea (OSA), and restless leg syndrome.^{128,129} The male-to-female prevalence of OSA is a 2:1 ratio in the general population,¹³⁰ but 8:1 or greater in clinical populations.¹³¹ Postmenopausal females are three times more likely than premenopausal females to have OSA.¹³² Biological contributors to sex-specific sleep differences include the hormonal and physical changes that females experience across the menopausal transition. Indeed, menopause influences the risk of sleep complaints, with up to 26% of peri-menopausal and post-menopausal females experiencing symptoms that fit the diagnosis of insomnia.¹³³ Hormones have specific physiological consequences that could explain the risks for sleep disorders. Progesterone has a sedating effect and can stimulate the ventilatory drive. Estrogen contributes to upper airway changes, including hyperemia, mucosal edema, and increased mucus secretion, leading to more upper airway resistance.¹³⁴ Another potential explanation for the sex differences in sleep disorders is the differences in the prevalence of risk factors for certain sleep disorders. Sleep disturbances, for example, can accompany anxiety and depression, which are more common in females than males.¹³⁵

5.3 | Depression

Depression is a well-established risk factor for ADRD; however, the relationship of depression to AD is likely complex and not fully understood.¹³⁶⁻¹³⁸ The literature has identified different hypotheses regarding this relationship including: (1) depression being a causative factor for ADRD, (2) depression being a characteristic of the ADRD prodrome, (3) depression being a reaction to the perception of cognitive decline, and (4) depression and ADRD sharing common biological mechanisms that may contribute to their conjoint prevalence. There is strong evidence supporting all hypotheses, suggesting that they are not mutually exclusive. Notably, most research examining depression and ADRD has been conducted in HICs, and has not adequately considered sociocultural perspectives in the assessment, and diagnosis, of depression. This is a major limitation because depressive-like symptoms are differentially expressed and experienced by people worldwide and across cultures.^{139,140} It has been suggested that there are countries/regions where words for depression do not exist.¹⁴¹

Depression is an ADRD risk factor that occurs more often in females. In 2017, an estimated 17.3 million adults in the United States had at least one major depressive episode, including 8.7% of females and 5.3% of males.¹⁴² Sex differences in depression can begin in early adolescence and persist through midlife, corresponding to the reproductive years in females. A possible reason for the female susceptibility to depression is the changes in estrogen and progesterone that become more pronounced during puberty and also change during pregnancy. This vulnerability carries through peri-menopause, often as recurrent episodes, when most depressive episodes occur.¹⁴³ Environmental exposures may also contribute to gender differences in the prevalence of depression. Lower SES status among women, gender differences in socialization, and higher rates of abuse and different coping styles in women, compared to men, may increase their susceptibility to depression and subsequently to ADRD.¹⁴⁴

5.4 | Diet and physical activity

Sex and gender differences in diet exist due to physiological, psychological, and sociocultural factors, as well as to behavioral norms.¹⁴⁵⁻¹⁴⁷ Dietary requirements vary by sex due to differences in metabolism, body fat distribution, and physiological needs (eg, pregnancy). However, few population-based studies have assessed whether relationships between diet and ADRD differ by sex or gender. Some studies reported that a diet low in vitamin B12 (indicated by serum methylmalonic acid)¹⁴⁸ or flavonols,¹⁴⁹ high in red meat and fat²⁸ or western dietary patterns¹⁵⁰ were associated with an increased risk of ADRD in men but not women. In contrast, vitamin E¹⁵¹ intake was associated with a greater reduction in risk of ADRD for women than men.

Women exercise less than men, on average, across the lifespan. This is due, in part, to gender roles such as parenthood and caregiving as well as a lack of encouragement of physical activity for women historically, and still in some cultures.^{152,153} Physical inactivity in the teenage years is associated with obesity and diabetes,¹⁵⁴ both of which are risk factors for ADRD and pose a greater risk for women.¹⁵⁵ Several studies have suggested that sex modifies the association between physical activity and cognition. Older women undergoing aerobic training showed greater cognitive gains than older men.¹⁵⁶⁻¹⁵⁸ Similarly, the Health, Aging, and Body Composition study reported that physical activity maintenance over 10 years predicted less decline in executive functions and processing speed among women, but not men.¹⁵⁹ These studies suggest that women may benefit more from exercise to enhance and maintain cognitive health.

5.5 | Traumatic brain injury (TBI)

Few studies have assessed whether the relationship between TBI and ADRD risk differs by sex,¹⁶⁰ and the evidence has been mixed.¹⁶¹⁻¹⁶⁶ This may be because adverse health and psychosocial factors throughout the lifespan moderate the risk of ADRD following TBI.¹⁶⁷⁻¹⁷² For example, greater exposure to adverse childhood experiences earlier in life has been observed as a risk factor for both TBI and other poor health behaviors and outcomes that interact throughout life to increase ADRD risk.^{170,173} Many of the overlapping adverse psychosocial risk factors for TBI disproportionately affect women, whereas sports and occupations, two of the biggest risks for TBI, differentially impact men.¹⁷⁴⁻¹⁷⁶ In addition, women are at greater risk for poorer health-related outcomes, including ADRD, even at equivalent levels of these psychosocial risk factors.⁴⁹ Few studies of TBI and dementia have been conducted in LMICs, where TBI rates are often higher than HICs and few resources for treatment are available. For example, in Pakistan, domestic violence against women, which sometimes results in head trauma, is a significant problem.¹⁷⁷ In addition, poor safety conditions, frequent incidents of terrorism, and political violence also contribute to the high rates of TBI in Pakistan.¹⁷⁷

5.6 | Pain

Global estimates of pain vary substantially across countries, ranging from ≈10% to 50%.¹⁷⁸ Country level factors associated with pain include income inequality (Gini index), higher population density, gender inequality, lower life expectancy, and region.¹⁷⁸ About 34% of adults in LMICs reported chronic pain, compared to 30% of adults in HICs.¹⁷⁹ Although there is increasing literature on pain as a potential risk factor for cognitive decline^{180,181} and ADRD risk,^{180,182-184} sex and gender differences have not been studied widely, and even less so across cultures. This is an important topic because females report more frequent and longer-lasting pain episodes, have more anatomically diffuse pain, and have higher pain sensitivity than men.^{185,186} Women

also have a greater analgesic response to mu-opioid antagonists and mixed action opioids, and they experience more adverse side effects from acute opioid use.^{187,188} Gender also influences patient-provider interactions that influence pain treatment and treatment response.¹⁸⁶ Pain interference (ie, challenges in performing daily, social, or work-related tasks due to pain), rather than intensity, may predict ADRD risk, but longitudinal studies are needed.¹⁸⁴ Recent work also suggests that pain may not be a risk factor for dementia but a prodromal symptom or correlate.¹⁸⁹ Chronic pain induces dysfunction of the locus coeruleus noradrenergic system and microglial pro-inflammatory activation resulting in neuroinflammation in areas of the brain that contribute to both pain and ADRD pathology.¹⁸² Sex or gender differences in the relationship of prescription opioid use—commonly used to treat pain—with cognition are mixed.^{190–193} Notably, most research on pain and cognition has been conducted in HICs, even though the majority of individuals who lack access to pain relief are in LMICs.¹⁹⁴

6 | SEX AND GENDER DIFFERENCES IN CLINICAL PRESENTATIONS (TABLE 5)

6.1 | Sex and gender differences in cognition and clinical diagnosis

Sex and gender differences in cognition exist throughout the lifespan. Females, on average, perform better on tests of verbal memory and processing speed, whereas males perform better on visuospatial tests.^{34,195–199} Language functions are associated closely with memory functions. However, little research has examined whether or how gender and sex differences in language functions occur in the development, diagnosis, or progression of ADRD.

Cultural factors can also impact performance on neuropsychological tests (see review in Ref. 200, including macrosocietal structures [eg, economics, sociopolitical history, government structures, and educational systems]) and individual characteristics, such as cultural values, race, ethnicity, SES status, language, educational attainment, literacy, and immigration history.^{201–203} Therefore, there is a need for valid tools and normative data to characterize cognitive functioning across culturally and linguistically diverse populations, to facilitate AD research worldwide. Similarly, performance on neuropsychological tests is influenced by an individual's lived experiences and education and learning opportunities. Low education levels have been identified as a risk factor for dementia,^{109,204,205} with known gender disparities in access to educational opportunities in both HICs and LMICs. Several measures have been developed to examine neurocognitive function in populations with high rates of illiteracy and/or low levels of formal education,²⁰⁶ including the Rowland Universal Dementia Assessment Scale,²⁰⁷ NEUROPSI,²⁰⁸ or the Figure Memory Test,²⁰⁹ although additional tools and normative data to be used in diverse cultural and geographical populations are still needed.²¹⁰ Female advantage on verbal memory tests has critical implications for early detection and intervention because clinical tests of cognitive function in older adults often do not consider sex differences.²¹¹ Thus, the verbal advantage for females could lead to a delayed diagnosis of MCI compared to males, and subse-

TABLE 5 Gaps in knowledge regarding sex differences in clinical presentation

Gaps in Knowledge

- More research is needed to further understand sex differences in cognitive decline in AD. Particularly, longitudinal studies with AD biomarker data are needed to track sex differences across the clinical trajectory of AD, since these differences seem to differ by disease/pathology stage.
- The generalizability of the female advantage in verbal memory across race/ethnicity groups is unclear, given that this work extends from predominantly White cohorts.^{34,195}
- More studies are needed to investigate how sex differences in the frequency and predictive utility of SCD influence MCI diagnostic rates and accuracy. Longitudinal studies are needed to address sex differences in the temporal pattern of changes in SCD in relation to cognitive decline.
- It remains unknown whether sex differences in neuropsychiatric symptoms are driven by different underlying neurobiological mechanisms. This could inform sex-specific treatment approaches, as it is currently unknown whether the response to pharmacological and non-pharmacological interventions that target neuropsychiatric symptoms differs by sex/gender.^{244,245}
- Uniform reporting of associations by sex is necessary to fully understand whether sex-specific cut-points of pathology markers for diagnosis or prognosis are needed.
- Further research is needed to better characterize sex differences in (1) the progression of AD pathology, (2) how the progression of different AD pathologies inter-relate, and (3) how progression of AD pathology relates to cognitive decline across disease stages.
- Few studies have examined sex differences in other factors that could contribute to differences in biomarker levels between females and males. For example, blood-brain barrier permeability is greater in males than females, starting around the age of 6 years,²⁷⁷ and can impact the concentrations of both blood and CSF-related biomarkers.

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; SCD, subjective cognitive decline.

quently to a more rapid rate of deterioration and diagnosis of dementia for females. Sex-specific norms have been developed,²¹² which improved the identification and diagnosis of memory impairment in both males and females in studies within the United States.²¹³ However, these norms have not been widely adopted. In addition, although there is some evidence that the female advantage in verbal memory generalizes across race/ethnic groups,^{34,195} it remains unknown how the application of sex-based norms impacts diagnostic accuracy in more diverse cohorts and in other global settings. The investment in early-life education and nutrition is crucial for later-life cognitive functioning. A recent study of the Harmonised Diagnostic Assessment of Dementia for the Longitudinal Aging Study in India (LASI-DAD) cohort (14 states in India) found that older Indian female adults had lower performance across most cognitive domains compared to their male counterparts; however, early-life SES, health, and education accounted for the performance gap.²¹⁴

Sex- and gender-specific shifts in the balance of resilience and risk factors to AD pathogenesis vary over the disease course. Although the sources of the sex and gender differences are not fully understood, possible explanations include: (1) a greater baseline verbal recall for older females than males of the same age, which subsequently requires a greater drop in recall for women to be detected; (2) a slower rate of cognitive decline for females than males; (3) a sex-specific vulnerability of critical brain structures (eg, hippocampal) that occurs earlier for males than females, resulting in greater impairment on verbal recall during initial disease stages for males; (4) sex-specific differences in cognitive reserve and compensatory mechanisms²¹⁵⁻²¹⁷; and/or (5) differences in functional connectivity such that females show greater efficiency in frontal executive networks, whereas males show greater efficiency in the posterior default mode network.²¹⁸

6.2 | Sex and gender differences in subjective cognitive decline (SCD)

Subjective changes in cognition or memory, commonly referred to as SCD or subjective memory complaints (SMCs),²¹⁹ are often a required component of MCI diagnosis. However, SCD may have different clinical meanings in women versus men in terms of the prognosis of AD. Few studies have examined this important question. Some studies in the United States and Europe suggest that the prevalence of SCD is higher for women than men,^{220,221} but not all.^{222,223} Moreover, the ability of SCD to predict objective impairment and dementia risk may differ by sex or gender. US-based studies found that, compared to males, SMC is more strongly associated with objective memory performance among females with amnesic MCI²²⁴ and with incident dementia among non-demented older adults followed over 15 years.²²¹ Similarly, in a Colombian cohort of cognitively unimpaired individuals with autosomal dominant AD and non-carrier family members, women had greater self-reported SCD than men.²²⁵ Study partner-reported SCD was also a stronger indicator of memory decline in women versus men. Few studies of SCD have been conducted in LMICs, partly because cognitive assessments have not been developed or validated and contribute to biases due to education, literacy, and culture.²²⁶ Using data from the 10/66 Dementia Research Group (26 study sites in India, China/Southeast Asia, Latin America, Nigeria, and Russia), SMC was highest in older adults with depression and dementia (independently) compared to controls.²²⁷ In addition, depression was correlated with SMC among older adults with and without dementia, emphasizing the intricate connection of mental and cognitive health, but sex and gender differences were not examined. Sex and gender differences in SCD and its prognostic utility could be due to biological and/or psychosocial factors, including differences in symptom perception or reporting^{228,229} and rates of depressive symptoms,²³⁰⁻²³² a known correlate of SCD.^{233,234} In addition, a more precipitous decline from MCI to AD in females may impact perceptibility.²³⁵ Overall, findings suggest the importance of considering sex and gender when clinically evaluating SCD.

6.3 | Sex and gender differences in neuropsychiatric symptoms (NPS)

Studies examining sex and gender differences in NPS in AD have yielded mixed findings. Some studies reported a higher burden of NPS for females with AD than males,^{236,237} whereas other studies did not find sex differences.^{238,239} When specific symptoms are examined, a higher prevalence of affective symptoms and psychotic symptoms among females and a higher prevalence of apathy and agitation among males has been reported.²⁴⁰⁻²⁴² Notably, a meta-analysis of 62 studies representing 21,554 patients with AD dementia failed to find associations between sex and total NPS burden, but did find that females with AD dementia had a greater presence and severity of depression, anxiety, psychotic symptoms (particularly delusions), and aberrant motor behavior, whereas apathy was more severe among males.²⁴³

6.4 | Sex and gender differences in neuroimaging and fluid-based biomarkers of AD pathology

Some studies report that women demonstrate a greater burden of AD pathology in the early disease stages.²⁴⁴⁻²⁴⁸ In contrast, other studies suggest that females have higher levels of brain glucose metabolism²⁴⁹ and greater cortical thickness.²⁵⁰ Thus, more research is needed to clarify sex-specific resilience and vulnerability to AD pathology across the clinical spectrum. Furthermore, sex may moderate the association between neuroimaging measures of AD pathology and cognitive function. For example, verbal memory performance among those with mild-to-moderate, but not severe, AD pathology is better for females than males. This pattern of findings has been reported for multiple AD-related neuroimaging biomarkers including hippocampal atrophy volume,²⁴⁹ amyloid positron emission tomography (PET),²⁵⁰⁻²⁵³ brain glucose hypometabolism²⁵⁴ and postmortem tau pathology.²⁵⁵ Similarly, research among individuals at genetic risk for autosomal-dominant AD from a Colombian cohort suggests that females may also have greater cognitive resilience to AD pathology and neurodegeneration than males.²⁵⁶

Fluid-based biomarkers of AD include low cerebrospinal fluid (CSF) or blood A β 42 or the A β 42/A β 40 ratio as a marker of amyloid pathology, elevated CSF, or blood phosphorylated tau (P-tau) as markers of neurofibrillary tangle pathology, and elevated CSF or blood total tau (T-tau) or neurofilament light chain (NfL) as markers of neurodegeneration.²⁵⁷ Most studies of blood and CSF AD biomarkers have adjusted for sex, with few examining sex differences.²⁵⁸ Regarding CSF biomarkers, studies consistently show higher levels of NfL, a marker of large-caliber subcortical axonal degeneration, across the lifespan in males.^{259,260} In contrast, an analysis of 10 longitudinal cohort studies reported that females have higher CSF T-tau levels than males.²⁴⁶ Cross-sectionally, studies of A β 42 or the A β 42/A β 40 ratio and P-tau have not reported sex differences in CSF levels.²⁶¹⁻²⁶⁵ However, females with low CSF A β 42 may be more susceptible to

increased CSF P-tau levels.²⁶⁴ Despite the consistently higher levels of CSF NfL in males, studies of plasma or serum NfL generally do not find sex differences.^{266,267} The reason for this discrepancy is not known. Three studies reported higher plasma T-tau levels for females,²⁶⁷⁻²⁶⁹ but other studies have not observed a sex difference for plasma T-tau,^{270,271} A β 42/40,^{272,273} or P-tau.²⁷⁴

7 | DISCUSSION AND FUTURE DIRECTIONS

Numerous studies of ADRD incidence have been conducted worldwide. However, few studies report estimates by sex or gender, or test for sex differences, and even fewer evaluate gender in the context of ADRD risk. Most studies that have examined sex and gender differences have been conducted in US and European cohorts. The extent to which selective survival bias and gender-related factors vary by country and culture, and explain conflicting results in gender and sex differences across countries, has not been well studied. Thus, more geographically and culturally representative studies of ADRD epidemiology examining both sex and gender differences are needed. Identifying geographic drivers of sex and gender differences in ADRD is a first step in developing interventions unique to each region to reduce these inequities and to ultimately reduce ADRD risk. These drivers may be biological or social/cultural in nature, and thus will require interventions at the societal, interpersonal, and/or biological levels. In scenarios where the identified drivers are structural and appear unmodifiable, the pursuit of health equity may be achieved by intervening in mechanisms linking the exposure to poor brain health through public health policies.

Many areas of the world do not have adequate estimates of the prevalence of ADRD because most studies have been conducted in HICs. This situation has resulted in a lack of replication of many dementia models developed in HICs to LMICs, likely due to HIC models neglecting the role of social and structural determinants of health, which accounts for >50% of a country's health outcomes.^{275,276} In addition, the lack of studies in some regions is compounded by minimal data collection in challenging settings, failure to collaborate with community stakeholders, and a lack of culturally relevant studies and sensitive measures.²²⁶ The new realities brought on by rapid globalization, international migration, escalating geopolitical conflicts, and transnationalism require a deep, focal examination of how sex and gender evolves to impact ADRD in LMICs. Future studies need to employ mixed methodologies to study how the constructs of sex and gender vary in behavioral roles and norms across cultural settings and their complex intersection with aging across the life course.

In summary, this review emphasizes the need to expand the definitions of gender and sex, consider sociocultural factors that lead to gender inequities in ADRD, and examine gender and sex differences in AD incidence, risk factors, and clinical presentations worldwide (Table 6). Identifying the drivers of ADRD inequities across sexes and genders will provide the foundation for future interventions aiming to improve healthy brain aging for all.

TABLE 6 Recommendations for future research of sex and gender differences in Alzheimer's disease and related dementias (ADRD)

Recommendations
<ul style="list-style-type: none"> Diagnostic assessments of ADRD should consider availability and access to health care (type, frequency) across the lifespan to contextualize prevalence and incidence across countries.
<ul style="list-style-type: none"> Gender and sex differences should be examined through multidimensional models that incorporate measures of health disparities, disability, stereotypes, and stigma/bias.
<ul style="list-style-type: none"> The lack of discussion of sex and gender in underrepresented and underserved populations reflects the inadequacy of the research on these populations, not their lack of existence or importance.
<ul style="list-style-type: none"> There is a need for more research examining the intersectionality of race/ethnicity, sex/gender, and sociocultural factors in AD risk factors and clinical presentations in diverse populations worldwide.
<ul style="list-style-type: none"> More culturally appropriate training to enhance strategies for engaging diverse populations in dementia research and care.
<ul style="list-style-type: none"> Development of cross-cultural valid and reliable measures to gather data.

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CONFLICTS OF INTEREST

Dr. Mielke has consulted for Biogen, Brain Protection Company and Labcorp unrelated to this manuscript. She is a Senior Associate Editor

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