Received: 23 December 2021 | Revised: 15 February 2022 | Accepted: 20 February 2022

DOI: 10.1002/alz.12662

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

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-Castelar[5] | Puja Agarwal[4,6] | Eider M. Arenaza-Urquijo[7,8,9] | Benjamin Brett[10] | Anna Brugulat-Serrat[7,8,9,11] | Lyndsey E. DuBose[12] | Willem S. Eikelboom[13] | Jason Flatt[14] | Nancy S. Foldi[15,16] | Sanne Franzen[13] | Paola Gilsanz[17] | Wei Li[18] | Alison J. McManus[19] | Debora Melo van Lent[20,21,22] | Sadaf Arefi Milani[23] | C. Elizabeth Shaaban[24] | Shana D. Stites[25] | Erin Sundermann[26] | Vidyani Suryadevara[27] | Jean-Francoise Trani[28] | Arlener D. Turner[29] | 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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[21]Framingham Heart Study, Framingham, Massachusetts, USA

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

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

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

[25]Department of Psychiatry, Perlman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

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

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

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

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

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

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

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

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

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

[35]Department 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.

Funding information
National Institutes of Health/National Institute on Aging, Grant/Award Numbers: RF1 AG55151 (MMM), U54 AG44170 (MMM), R01AG068183 (GMB), R01AG067428 (GMB), R01AG074302 (GMB), F32AG071273 (LED), T32AG000279 (LED), R01AG062637 (NTA), R01AG073627 (NTA), P30AG010161 (NTA), P30AG072975 (NTA), T32AG055381 (CES), R03 AG 67062 (DMVL), K23 AG073528 (BB), P30AG059301 (SAM), P30AG024832 (SAM), K23AG065442 (SDS), K99AG066934 (JMJV), R01 AG054671 (YTQ), 5R01AG066823 (YTQ); National Institutes of Health/National Institute of General Medical Sciences, Grant/Award Number: SC3GM122662 (NSF); National Institutes of Health/Office of the Director National Institute of Allergy and Infectious Diseases, and Eunice Kennedy Shriver National Institute of Child Health & Human Development Building Interdisciplinary Research Careers in Women's Health Program, Grant/Award Numbers: BIRCWH, K12HD052023 (SAM); National Institutes of Health/National Institute of Neurological Disorders and Stroke, Grant/Award Number: L30NS113158 (BB); National Institutes of Health/Office of the Director, Grant/Award Number: DP5OD019833 (YTQ); Alzheimer's Association, Grant/Award Numbers: AARF 2019A005859 (CVC), AARG-21-852512 (PA), 2019-AARGD-644788 (PG), AARF-17-528934 (SDS); BrightFocus Foundation, Grant/Award Number: A2021142S (GMB); Ludeman Family Center for Women's Health Research Early-Career Faculty Research Development Award (LED); Massachusetts General Hospital ECOR; Alzheimer Nederland Fellowship, Grant/Award Number: WE.15-2018-05 (J.M.J.V); NWO/ZonMw Veni, Grant/Award Number: 09150161810017 (J.M.J.V)

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 Europe[12–16] 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]

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.

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 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 tests[79] 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 (Aβ) 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 injuy.

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] Post-menopausal females are three times more likely than pre-menopausal 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 fat[28] or western dietary patterns[150] were associated with an increased risk of ADRD in men but not women. In contrast, vitamin E[151] 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 disproportionally 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 subsequently 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]

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.

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 mechanisms[215–217]; 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 ADRD. 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 amnestic MCI[224] 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 ADRD have yielded mixed findings. Some studies reported a higher burden of NPS for females with ADRD 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 metabolism[249] 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 hypometabolism[254] 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 Aβ42 or the Aβ42/Aβ40 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 Aβ42 or the Aβ42/Aβ40 ratio and P-tau have not reported sex differences in CSF levels.[261–265] However, females with low CSF Aβ42 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] Aβ42/40,[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
• Diagnostic assessments of ADRD should consider availability and access to health care (type, frequency) across the lifespan to contextualize prevalence and incidence across countries.
• Gender and sex differences should be examined through multidimensional models that incorporate measures of health disparities, disability, stereotypes, and stigma/bias.
• 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.
• 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.
• More culturally appropriate training to enhance strategies for engaging diverse populations in dementia research and care.
• Development of cross-cultural valid and reliable measures to gather data.

ACKNOWLEDGMENTS

This project was supported by grants from the National Institutes of Health/National Institute on Aging: RF1 AG55151 (MMM), U54 AG44170 (MMM), R01AG068183 (GMB), R01AG067428 (GMB), R01AG074302 (GMB), F32AG071273 (LED), T32AG000279 (LED), R01AG062637 (NTA), R01AG073627 (NTA), P30AG010161 (NTA), P30AG072975 (NTA), T32AG055381 (CES), R03 AG 67062 (DMVL), K23 AG073528 (BB), P30AG059301 (SAM), P30AG024832 (SAM), K23AG065442 (SDS), K99AG066934 (JMJV), R01 AG054671 (YTQ), and 5R01AG066823 (YTQ); National Institutes of Health/National Institute of General Medical Sciences: SC3GM122662 (NSF); National Institutes of Health/Office of the Director National Institute of Allergy and Infectious Diseases, and Eunice Kennedy Shriver National Institute of Child Health & Human Development Building Interdisciplinary Research Careers in Women's Health Program-BIRCWH: K12HD052023 (SAM); National Institutes of Health/National Institute of Neurological Disorders and Stroke: L30NS113158 (BB); National Institutes of Health/Office of the Director: DP5OD019833 (YTQ); Alzheimer's Association: AARF 2019A005859 (CVC); AARG-21-852512 (PA); 2019-AARGD-644788 (PG); AARF-17-528934 (SDS); BrightFocus Foundation: A2021142S (GMB); Ludeman Family Center for Women's Health Research Early-Career Faculty Research Development Award (LED); Massachusetts General Hospital ECOR (YTQ); Alzheimer Nederland Fellowship: WE.15-2018-05 (J.M.J.V); and NWO/ZonMw Veni: Grant project number 09150161810017 (J.M.J.V).

CONFLICTS OF INTEREST

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

for *Alzheimer's and Dementia: The Journal of the Alzheimer's Association*. All other authors report no conflicts of interest.

REFERENCES

1. Prince MJ, Wimo A, Guerchet MM, Ali GC, Wu Y-T, Prina M. *World Alzheimer Report 2015 - The Global Impact of Dementia: An Analysis of Prevalence, Incidence, Cost and Trends*. London: Alzheimer's Disease International; 2015:84.
2. *United Nations-Department of Economic and Social Affairs-Population Division. Population Division (2015)*. World Population Ageing; 2015; ST/ESA/SER.A/390
3. Rocca WA, Cha RH, Waring SC, Kokmen E. Incidence of dementia and Alzheimer's disease: a reanalysis of data from Rochester, Minnesota, 1975-1984. *Am J Epidemiol*. 1998;148:51-62.
4. Bachman DL, Wolf PA, Linn RT, et al. Incidence of dementia and probable Alzheimer's disease in a general population: the Framingham Study. *Neurology*. 1993;43:515-519.
5. Ganguli M, Dodge HH, Chen P, Belle S, DeKosky ST. Ten-year incidence of dementia in a rural elderly US community population: the MoVIES Project. *Neurology*. 2000;54:1109-1116.
6. Kawas C, Gray S, Brookmeyer R, Fozard J, Zonderman A. Age-specific incidence rates of Alzheimer's disease: the Baltimore Longitudinal Study of Aging. *Neurology*. 2000;54:2072-2077.
7. Hebert LE, Scherr PA, McCann JJ, Beckett LA, Evans DA. Is the risk of developing Alzheimer's disease greater for women than for men? *Am J Epidemiol*. 2001;153:132-136.
8. Kukull WA, Higdon R, Bowen JD, et al. Dementia and Alzheimer disease incidence: a prospective cohort study. *Arch Neurol*. 2002;59:1737-1746.
9. Edland SD, Rocca WA, Petersen RC, Cha RH, Kokmen E. Dementia and Alzheimer disease incidence rates do not vary by sex in Rochester, Minn. *Arch Neurol*. 2002;59:1589-1593.
10. Maestre GE, Mena LJ, Melgarejo JD, et al. Incidence of dementia in elderly Latin Americans: results of the Maracaibo Aging Study. *Alzheimers Dement*. 2018;14:140-147.
11. Tyas SL, Tate RB, Wooldrage K, Manfreda J, Strain LA. Estimating the incidence of dementia: the impact of adjusting for subject attrition using health care utilization data. *Ann Epidemiol*. 2006;16:477-484.
12. Fratiglioni L, Viitanen M, von Strauss E, Tontodonati V, Herlitz A, Winblad B. Very old women at highest risk of dementia and Alzheimer's disease: incidence data from the Kungsholmen Project, Stockholm. *Neurology*. 1997;48:132-138.
13. Ott A, Breteler MM, van Harskamp F, Stijnen T, Hofman A. Incidence and risk of dementia. The Rotterdam Study. *Am J Epidemiol*. 1998;147:574-580.
14. Letenneur L, Gilleron V, Commenges D, Helmer C, Orgogozo JM, Dartigues JF. Are sex and educational level independent predictors of dementia and Alzheimer's disease? Incidence data from the PAQUID project. *J Neurol Neurosurg Psychiatry*. 1999;66:177-183.
15. Andersen K, Launer LJ, Dewey ME, et al. Gender differences in the incidence of AD and vascular dementia: the EURODEM Studies. EURODEM Incidence Research Group. *Neurology*. 1999;53:1992-1997.
16. Ruitenberg A, Ott A, van Swieten JC, Hofman A, Breteler MM. Incidence of dementia: does gender make a difference? *Neurobiol Aging*. 2001;22:575-580.
17. Yoshitake T, Kiyohara Y, Kato I, et al. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study. *Neurology*. 1995;45:1161-1168.
18. Liu CK, Lai CL, Tai CT, Lin RT, Yen YY, Howng SL. Incidence and subtypes of dementia in southern Taiwan: impact of socio-demographic factors. *Neurology*. 1998;50:1572-1579.
19. Matthews FE, Stephan BC, Robinson L, et al. A two decade dementia incidence comparison from the cognitive function and ageing studies I and II. *Nat Commun*. 2016;7:11398.
20. Mielke MM, Vemuri P, Rocca WA. Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences. *Clin Epidemiol*. 2014;6:37-48.
21. Rocca WA, Mielke MM, Vemuri P, Miller VM. Sex and gender differences in the causes of dementia: a narrative review. *Maturitas*. 2014;79:196-201.
22. Bloomberg M, Dugravot A, Dumurgier J, et al. Sex differences and the role of education in cognitive ageing: analysis of two UK-based prospective cohort studies. *Lancet Public Health*. 2021;6:e106-e115.
23. Mayeda ER, Mobley TM, Weiss RE, Murchland AR, Berkman LF, Sabbath EL. Association of work-family experience with mid- and late-life memory decline in US women. *Neurology*. 2020;95:e3072-e3080.
24. Biscardi M, Colantonio A. Sex, *Gender, and Cultural Considerations for Rehabilitation Research with Older Adults. Handbook of Rehabilitation in Older Adults. Handbooks in Health, Work, and Disability*. Gatchel RJ, Schultz IZ, Ray CT, eds. Switerzerland: Springer, Cham; 2018:519-537.
25. Institute of Medicine. *Exploring the Biological Contributions to Human Health: Does Sex Matter?*. Wizemann TM, Pardue ML, eds. Washington, DC: The National Academies Press; 2001.
26. Office of Research on Women's Health. *Including Women and Minorities in Clinical Research*. Office of Research on Women's Health; 2022.
27. Ainsworth C. Sex redefined. *Nature*. 2015;518:288-291.
28. Flatt J. The epidemiology of dementia in LGBTQ older adults. *Innov Aging*. 2020;4:748-749.
29. American Psychological A. Guidelines for psychological practice with lesbian, gay, and bisexual clients. *Am Psychol*. 2012;67:10-42.
30. Kinsey AC, Pomeroy WB, Martin CE, Gebhard PH. *Sexual Behavior in the Human Female*. Bloomington: Indiana University Press; 1998.
31. Klein F, Sepekoff B, Wolf TJ. Sexual orientation: a multi-variable dynamic process. *J Homosex*. 1985;11:35-49.
32. Weinrich JD, Snyder PJ, Pillard RC, et al. A factor analysis of the Klein sexual orientation grid in two disparate samples. *Arch Sex Behav*. 1993;22:157-168.
33. Flatt JD, Cicero EC, Kittle KR, Brennan-Ing M. Recommendations for advancing research with sexual and gender minority older adults. *J Gerontol B Psychol Sci Soc Sci*. 2022;77:1-9.
34. Avila JF, Vonk JMJ, Verney SP, et al. Sex/gender differences in cognitive trajectories vary as a function of race/ethnicity. *Alzheimers Dement*. 2019;15:1516-1523.
35. Koch JM, McLachlan Ct, Victor CJ, Westcott J, Yager C. The cost of being transgender: where socio-economic status, global health care systems, and gender identity intersect. *Psychol Sex*. 2020;11:103-119.
36. Messerschmidt JW, Yancey Martin P, Messner MA, Connell R. *Gender Reckonings: New Social Theory and Research*. New York, NY: New York University Press; 2018.
37. Morgenroth T, Ryan MK. The effects of gender trouble: an integrative theoretical framework of the perpetuation and disruption of the gender/sex binary. *Perspect Psychol Sci*. 2021;16:1113-1142.
38. Stites SD, Cao H, Harkins K, Flatt JD. Measuring sex and gender in aging and Alzheimer's research: results of a national survey. *J Gerontol B Psychol Sci Soc Sci*. 2021;2021:gbab226.
39. Tan JY, Baig AA, Chin MH. High stakes for the health of sexual and gender minority patients of color. *J Gen Intern Med*. 2017;32:1390-1395.
40. Ayhan CHB, Bilgin H, Uluman OT, Sukut O, Yilmaz S, Buzlu S. A systematic review of the discrimination against sexual and gender minority in health care settings. *Int J Health Serv*. 2020;50:44-61.
41. Shively MG, De Cecco JP. Components of sexual identity. *J Homosex*. 1977;3:41-48.

42. Alex L, Fjellman Wiklund A, Lundman B, Christianson M, Hammarstrom A. Beyond a dichotomous view of the concepts of 'sex' and 'gender' focus group discussions among gender researchers at a medical faculty. *PLoS One*. 2012;7:e50275.
43. Maccora J, Peters R, Anstey KJ. What does (low) education mean in terms of dementia risk? A systematic review and meta-analysis highlighting inconsistency in measuring and operationalising education. *SSM Popul Health*. 2020;12:100654.
44. Xu W, Tan L, Wang HF, et al. Education and risk of dementia: dose-response meta-analysis of prospective cohort studies. *Mol Neurobiol*. 2016;53:3113-3123.
45. Gilsanz P, Mayeda ER, Eng CW, et al. Participant education, spousal education and dementia risk in a diverse cohort of members of an integrated health care delivery system in Northern California. *BMJ Open*. 2021;11:e040233.
46. Letenneur L, Launer LJ, Andersen K, et al. Education and the risk for Alzheimer's disease: sex makes a difference. EURODEM pooled analyses. EURODEM Incidence Research Group. *Am J Epidemiol*. 2000;151:1064-1071.
47. Madigan JC. The education of girls and women in the United States: a historical perspective. *Adv Gender Educ*. 2009;1:11-13.
48. United Nations Children's Fund-UN Women and Plan International. *A New Era for Girls: Taking Stock of 25 Years of Progress*. New York: United Nations Children's Fund-UN Women and Plan International; 2020.
49. Hasselgren C, Ekbrand H, Hallerod B, et al. Sex differences in dementia: on the potentially mediating effects of educational attainment and experiences of psychological distress. *BMC Psychiatry*. 2020;20:434.
50. Bakhshi P, Babulal GM, Trani JF. Education of children with disabilities in New Delhi: when does exclusion occur? *PLoS One*. 2017;12:e0183885.
51. Bakhshi P, Babulal GM, Trani J-F. Education and disability in a conflict affected context: are children with disabilities less likely to learn and be protected in Darfur? *World Dev*. 2018;106:248-259.
52. Bakhshi P, Babulal GM, Trani J-F. Disability, poverty, and schooling in post-civil war in Sierra Leone. *Eur J Devel Res*. 2021;33:482-501.
53. Klugman J, Hanmer L, Twigg S, Hasan T, McCleary-Sills J, Santamaria J. *Voice and Agency: Empowering Women and Girls for Shared Prosperity*. Washington, DC: World Bank; 2014. License: Creative Commons Attribution CC BY 3.0 IGO.
54. Blumberg RL. *Gender Bias Textbooks: A Hidden Obstacle on the Road to Gender Equality in Education*. United Nations Educational, Scientific, and Cultural Organization (UNESCO); 2007:1-54.
55. United Nations-Educational Scientific and Cultural Organisation. *2007 EFA Global Monitoring Report: Strong Foundations: Early Childhood Care and Education*. Paris: UNESCO Publishing; 2006.
56. Islam KMM, Asadullah MN. Gender stereotypes and education: a comparative content analysis of Malaysian, Indonesian, Pakistani and Bangladeshi school textbooks. *PLoS One*. 2018;13:e0190807.
57. Jones MA, Kitetu C, Sunderland J. Discourse roles, gender and language textbook dialogues: who learns what from John and Sally? *Gender Educ*. 1997;9:469-490.
58. Hamid BDHA, Yasin MSM, Bakar KA, Keong YC, Halaluddin A. Linguistic sexism and gender role stereotyping In Malaysian English language textbooks. *GEMA Online J Lang Stud*. 2008;8:45-78.
59. Kabeer N. Gender equality and women's empowerment: a critical analysis of the third millennium development goal 1. *Gender Dev*. 2005;13:13-24.
60. U.S. Bureau of Labor Statistics. *Women in the Labor Force: A Databook*. *BLS Reports. Report 1065*. U.S. Bureau of Labor Statistics; 2017.
61. Roos PA, Stevens LM. Integrating occupations: changing occupational sex segregation in the United States from 2000 to 2014. *Demogr Res*. 2018;38:127-154.
62. Huang LY, Hu HY, Wang ZT, et al. Association of occupational factors and dementia or cognitive impairment: a systematic review and meta-analysis. *J Alzheimers Dis*. 2020;78:217-227.
63. Helmer C, Letenneur L, Rouch I, et al. Occupation during life and risk of dementia in French elderly community residents. *J Neurol Neurosurg Psychiatry*. 2001;71:303-309.
64. Qiu C, Karp A, von Strauss E, Winblad B, Fratiglioni L, Bellander T. Lifetime principal occupation and risk of Alzheimer's disease in the Kungsholmen project. *Am J Ind Med*. 2003;43:204-211.
65. Andel R, Crowe M, Hahn EA et al. Work-related stress may increase the risk of vascular dementia. *J Am Geriatr Soc*. 2012;60:60-67.
66. Hasselgren C, Dellve L, Ekbrand H, et al. Socioeconomic status, gender and dementia: the influence of work environment exposures and their interactions with APOE varepsilon4. *SSM Popul Health*. 2018;5:171-179.
67. Ford KJ, Batty GD, Leist AK. Examining gender differentials in the association of low control work with cognitive performance in older workers. *Eur J Public Health*. 2021;31:174-180.
68. Evanoff B, Yung M, Buckner-Petty S, et al. Cross-national comparison of two general population job exposure matrices for physical work exposures. *Occup Environ Med*. 2019;76:567-572.
69. Hosang GM, Bhui K. Gender discrimination, victimisation and women's mental health. *Br J Psychiatry*. 2018;213:682-684.
70. McCarthy J. *Six in 10 Americans Worry about Higher Healthcare Premiums*. Gallup News Brief; 2018.
71. Schmittdiel JA, Steers N, Duru OK, et al. Patient-provider communication regarding drug costs in Medicare Part D beneficiaries with diabetes: a TRIAD Study. *BMC Health Serv Res*. 2010;10:164.
72. Yelverton V, Qiao S, Menon JA, et al. Criminalization of sexual and gender minorities and Its consequences for the HIV epidemic in Zambia: a critical review and recommendations. *J Assoc Nurses AIDS Care*. 2021;32:423-441.
73. Currier A, McKay T. Pursuing social justice through public health: gender and sexual diversity activism in Malawi. *Crit Afr Stud*. 2017;9:71-90.
74. Kachen A, Pharr JR. Health care access and utilization by transgender populations: a United States transgender survey study. *Transgend Health*. 2020;5:141-148.
75. Grant JM, Mottet LA, Tanis J, Harrison J, Herman JL, Keisling M. *Injustice at Every Turn: A Report of the National Transgender Discrimination Survey*. Washington: National Center for Transgender Equality and National Gay and Lesbian Task Force; 2011.
76. Meyer IH, Brown TN, Herman JL, Reisner SL, Bockting WO. Demographic characteristics and health status of transgender adults in select US regions: behavioral risk factor surveillance system, 2014. *Am J Public Health*. 2017;107:582-589.
77. Thoreson RR. Troubling the waters of a 'wave of homophobia': political economies of anti-queer animus in sub-Saharan Africa. *Sexualities*. 2014;17:23-42.
78. Nama N, MacPherson P, Sampson M, McMillan HJ. Medical students' perception of lesbian, gay, bisexual, and transgender (LGBT) discrimination in their learning environment and their self-reported comfort level for caring for LGBT patients: a survey study. *Med Educ Online*. 2017;22:1368850.
79. Mielke MM. Sex and gender differences in Alzheimer's disease dementia. *Psychiatr Times*. 2018;35:14-47.
80. Wang W, Xie X, Yuan T, et al. Epidemiological trends of maternal hypertensive disorders of pregnancy at the global, regional, and national levels: a population-based study. *BMC Pregnancy Childbirth*. 2021;21:364.
81. Mielke MM, Milic NM, Weissgerber TL, et al. Impaired cognition and brain atrophy decades after hypertensive pregnancy disorders. *Circ Cardiovasc Qual Outcomes* 2016;9:S70-S76.

82. Siepmann T, Boardman H, Bilderbeck A, et al. Long-term cerebral white and gray matter changes after preeclampsia. *Neurology*. 2017;88:1256-1264.
83. Wiegman MJ, Zeeman GG, Aukes AM, et al. Regional distribution of cerebral white matter lesions years after preeclampsia and eclampsia. *Obstet Gynecol*. 2014;123:790-795.
84. Fields JA, Garovic VD, Mielke MM, et al. Preeclampsia and cognitive impairment later in life. *Am J Obstet Gynecol*. 2017;217:74. e1- e11.
85. Shaaban CE, Rosano C, Cohen AD, et al. Cognition and cerebrovascular reactivity in midlife women with history of preeclampsia and placental evidence of maternal vascular malperfusion. *Front Aging Neurosci*. 2021;13:637574.
86. Garovic VD, White WM, Vaughan L, et al. Incidence and long-term outcomes of hypertensive disorders of pregnancy. *J Am Coll Cardiol*. 2020;75:2323-2334.
87. Andolf EG, Sydsjo GC, Bladh MK, Berg G, Sharma S. Hypertensive disorders in pregnancy and later dementia: a Swedish National Register Study. *Acta Obstet Gynecol Scand*. 2017;96:464-471.
88. Basit S, Wohlfahrt J, Boyd HA. Pre-eclampsia and risk of dementia later in life: nationwide cohort study. *BMJ*. 2018;363:k4109.
89. Gervais NJ, Au A, Almey A, et al. Cognitive markers of dementia risk in middle-aged women with bilateral salpingo-oophorectomy prior to menopause. *Neurobiol Aging*. 2020;94:1-6.
90. Zeydan B, Tosakulwong N, Schwarz CG, et al. Association of bilateral salpingo-oophorectomy before menopause onset with medial temporal lobe neurodegeneration. *JAMA Neurol*. 2019;76:95-100.
91. Ryan J, Scali J, Carriere I, et al. Impact of a premature menopause on cognitive function in later life. *BJOG*. 2014;121:1729-1739.
92. Rocca WA, Bower JH, Maraganore DM, et al. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. *Neurology* 2007;69:1074-1083.
93. Bove R, Secor E, Chibnik LB, et al. Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women. *Neurology* 2014;82:222-229.
94. Rocca WA, Lohse CM, Smith CY, Fields JA, Machulda MM, Mielke MM. Association of premenopausal bilateral oophorectomy with cognitive performance and risk of mild cognitive impairment. *JAMA Netw Open*. 2021;4:e2131448.
95. Mosconi L, Rahman A, Diaz I, et al. Increased Alzheimer's risk during the menopause transition: a 3-year longitudinal brain imaging study. *PLoS One*. 2018;13:e0207885.
96. Gleason CE, Dowling NM, Wharton W, et al. Effects of hormone therapy on cognition and mood in recently postmenopausal women: findings from the Randomized, Controlled KEEPS-Cognitive and Affective Study. *PLoS Med*. 2015;12:e1001833; discussion e1001833.
97. Espeland MA, Shumaker SA, Leng I, et al. Long-term effects on cognitive function of postmenopausal hormone therapy prescribed to women aged 50 to 55 years. *JAMA Intern Med*. 2013;173:1429-1436.
98. Hamoda H. Availability of menopausal hormone therapy products worldwide. *Maturitas*. 2020;141:87-88.
99. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209-249.
100. Shahinian VB, Kuo YF, Freeman JL, Orihuela E, Goodwin JS. Increasing use of gonadotropin-releasing hormone agonists for the treatment of localized prostate carcinoma. *Cancer*. 2005;103:1615-1624.
101. Gonzalez BD, Jim HS, Booth-Jones M, et al. Course and predictors of cognitive function in patients with prostate cancer receiving androgen-deprivation therapy: a controlled comparison. *J Clin Oncol*. 2015;33:2021-2027.
102. Lehrer S, Rheinstein PH, Rosenzweig KE. No relationship of antiandrogens to Alzheimer's disease or cognitive disorder in the MedWatch Database. *J Alzheimers Dis Rep*. 2018;2:123-127.
103. Alibhai SM, Timilshina N, Duff-Canning S, et al. Effects of long-term androgen deprivation therapy on cognitive function over 36 months in men with prostate cancer. *Cancer*. 2017;123:237-244.
104. Jayadevappa R, Chhatre S, Malkowicz SB, Parikh RB, Guzzo T, Wein AJ. Association between androgen deprivation therapy use and diagnosis of dementia in men with prostate cancer. *JAMA Netw Open*. 2019;2:e196562.
105. Huang WK, Liu CH, Pang ST, et al. Type of androgen deprivation therapy and risk of dementia among patients with prostate cancer in Taiwan. *JAMA Netw Open*. 2020;3:e2015189.
106. Alonso-Quinones H, Stish BJ, Aakre JA, Hagen CE, Petersen RC, Mielke MM. Androgen deprivation therapy use and risk of mild cognitive impairment in prostate cancer patients. *Alzheimer Dis Assoc Disord*. 2021;35:44-47.
107. Feldman HA, Longcope C, Derby CA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts Male Aging Study. *J Clin Endocrinol Metab*. 2002;87:589-598.
108. Holland J, Bandelow S, Hogervorst E. Testosterone levels and cognition in elderly men: a review. *Maturitas*. 2011;69:322-337.
109. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396:413-446.
110. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol*. 2020;16:223-237.
111. Chui HC, Zheng L, Reed BR, Vinters HV, Mack WJ. Vascular risk factors and Alzheimer's disease: are these risk factors for plaques and tangles or for concomitant vascular pathology that increases the likelihood of dementia? An evidence-based review. *Alzheimers Res Ther*. 2012;3:1.
112. Feldstein CA. Effects of blood pressure changes on Alzheimer's disease. *Neuroepidemiology*. 2010;35:202-212.
113. Launer LJ, Ross GW, Petrovitch H, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. *Neurobiol Aging*. 2000;21:49-55.
114. Skoog I, Gustafson D. Hypertension, hypertension-clustering factors and Alzheimer's disease. *Neurol Res*. 2003;25:675-680.
115. Walker KA, Sharrett AR, Wu A, et al. Association of midlife to late-life blood pressure patterns with incident dementia. *JAMA* 2019;322:535-545.
116. Gilsanz P, Mayeda ER, Glymour MM, et al. Female sex, early-onset hypertension, and risk of dementia. *Neurology*. 2017;89:1886-1893.
117. Whitmer RA, Gunderson EP, Quesenberry CP, Jr., Zhou J, Yaffe K. Body mass index in midlife and risk of Alzheimer disease and vascular dementia. *Curr Alzheimer Res*. 2007;4:103-109.
118. Ramirez LA, Sullivan JC. Sex differences in hypertension: where we have been and where we are going. *Am J Hypertens*. 2018;31:1247-1254.
119. Blanken AE, Nation DA. Does gender influence the relationship between high blood pressure and dementia? Highlighting areas for further investigation. *J Alzheimers Dis*. 2020;78:23-48.
120. Gabin JM, Tambs K, Saltvedt I, Sund E, Holmen J. Association between blood pressure and Alzheimer disease measured up to 27 years prior to diagnosis: the HUNT Study. *Alzheimers Res Ther*. 2017;9:37.
121. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology*. 2005;64:277-281.
122. Kimm H, Lee PH, Shin YJ, et al. Mid-life and late-life vascular risk factors and dementia in Korean men and women. *Arch Gerontol Geriatr*. 2011;52:e117-e122.
123. George-Carey R, Adeloye D, Chan KY, et al. An estimate of the prevalence of dementia in Africa: a systematic analysis. *J Glob Health*. 2012;2:020401.
124. Jia L, Du Y, Chu L, et al. Prevalence, risk factors, and management of dementia and mild cognitive impairment in adults aged 60

years or older in China: a cross-sectional study. *Lancet Public Health*. 2020;5:e661-e671.
125. Santilli F, D'Ardes D, Guagnano MT, Davi G. Metabolic syndrome: sex-related cardiovascular risk and therapeutic approach. *Curr Med Chem*. 2017;24:2602-2627.
126. Gerdts E, Regitz-Zagrosek V. Sex differences in cardiometabolic disorders. *Nat Med*. 2019;25:1657-1666.
127. Institute of Medicine. *Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem*. Washington, DC: The National Academies Press; 2006.
128. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
129. Theorell-Haglow J, Miller CB, Bartlett DJ, Yee BJ, Openshaw HD, Grunstein RR. Gender differences in obstructive sleep apnoea, insomnia and restless legs syndrome in adults - What do we know? A clinical update. *Sleep Med Rev*. 2018;38:28-38.
130. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med*. 2002;165:1217-1239.
131. Young T, Hutton R, Finn L, Badr S, Palta M. The gender bias in sleep apnea diagnosis. Are women missed because they have different symptoms? *Arch Intern Med*. 1996;156:2445-2451.
132. Bixler EO, Vgontzas AN, Lin HM, et al. Prevalence of sleep-disordered breathing in women: effects of gender. *Am J Respir Crit Care Med* 2001;163:608-613.
133. Joffe H, Massler A, Sharkey KM. Evaluation and management of sleep disturbance during the menopause transition. *Semin Reprod Med*. 2010;28:404-421.
134. The NAMS Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause* 2017;24:728-53.
135. Krishnan V, Collop NA. Gender differences in sleep disorders. *Curr Opin Pulm Med*. 2006;12:383-289.
136. Barnes DE, Yaffe K, Byers AL, McCormick M, Schaefer C, Whitmer RA. Midlife vs late-life depressive symptoms and risk of dementia: differential effects for Alzheimer disease and vascular dementia. *Arch Gen Psychiatry*. 2012;69:493-498.
137. Brommelhoff JA, Gatz M, Johansson B, McArdle JJ, Fratiglioni L, Pedersen NL. Depression as a risk factor or prodromal feature for dementia? Findings in a population-based sample of Swedish twins. *Psychol Aging*. 2009;24:373-384.
138. Dafsari FS, Jessen F. Depression-an underrecognized target for prevention of dementia in Alzheimer's disease. *Transl Psychiatry*. 2020;10:160.
139. Haroz EE, Ritchey M, Bass JK, et al. How is depression experienced around the world? A systematic review of qualitative literature. *Soc Sci Med*. 2017;183:151-62.
140. Jang Y, Small BJ, Haley WE. Cross-cultural comparability of the Geriatric Depression Scale: comparison between older Koreans and older Americans. *Aging Ment Health*. 2001;5:31-37.
141. Manson SM. Culture and major depression. Current challenges in the diagnosis of mood disorders. *Psychiatr Clin North Am*. 1995;18:487-501.
142. Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the National Comorbidity Survey. I: lifetime prevalence, chronicity and recurrence. *J Affect Disord*. 1993;29:85-96.
143. Maki PM, Kornstein SG, Joffe H, et al. Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations. *J Womens Health (Larchmt)*. 2019;28:117-134.
144. Shors TJ, Millon EM, Chang HY, Olson RL, Alderman BL. Do sex differences in rumination explain sex differences in depression? *J Neurosci Res*. 2017;95:711-718.
145. Vari R, Scazzocchio B, D'Amore A, Giovannini C, Gessani S, Masella R. Gender-related differences in lifestyle may affect health status. *Ann Ist Super Sanita*. 2016;52:158-166.
146. Leblanc V, Begin C, Corneau L, Dodin S, Lemieux S. Gender differences in dietary intakes: what is the contribution of motivational variables? *J Hum Nutr Diet*. 2015;28:37-46.
147. Grzymislawska M, Puch EA, Zawada A, Grzymislawski M. Do nutritional behaviors depend on biological sex and cultural gender? *Adv Clin Exp Med*. 2020;29:165-172.
148. Tangney CC, Tang Y, Evans DA, Morris MC. Biochemical indicators of vitamin B12 and folate insufficiency and cognitive decline. *Neurology*. 2009;72:361-367.
149. Holland TM, Agarwal P, Wang Y, et al. Dietary flavonols and risk of Alzheimer dementia. *Neurology*. 2020;94:e1749-e1756.
150. D'Amico D, Parrott MD, Greenwood CE, et al. Sex differences in the relationship between dietary pattern adherence and cognitive function among older adults: findings from the NuAge study. *Nutr J*. 2020;19:58.
151. Beydoun MA, Fanelli-Kuczmarski MT, Kitner-Triolo MH, et al. Dietary antioxidant intake and its association with cognitive function in an ethnically diverse sample of US adults. *Psychosom Med*. 2015;77:68-82.
152. Verhoef MJ, Love EJ, Rose MS. Women's social roles and their exercise participation. *Women Health*. 1992;19:15-29.
153. Nomaguchi KM, Bianchi SM. Exercise time: gender differences in the effects of marriage, parenthood, and employment. *J Marriage Fam*. 2004;66:413-430.
154. McGavock J, Sellers E, Dean H. Physical activity for the prevention and management of youth-onset type 2 diabetes mellitus: focus on cardiovascular complications. *Diab Vascu Dis Res* 2007;4:305-310.
155. Luchsinger JA. Adiposity, hyperinsulinemia, diabetes and Alzheimer's disease: an epidemiological perspective. *Eur J Pharmacol*. 2008;585:119-129.
156. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci*. 2003;14:125-130.
157. Barha CK, Davis JC, Falck RS, Nagamatsu LS, Liu-Ambrose T. Sex differences in exercise efficacy to improve cognition: a systematic review and meta-analysis of randomized controlled trials in older humans. *Front Neuroendocrinol*. 2017;46:71-85.
158. Barha CK, Hsiung GR, Best JR, et al. Sex difference in aerobic exercise efficacy to improve cognition in older adults with vascular cognitive impairment: secondary analysis of a randomized controlled trial. *J Alzheimers Dis*. 2017;60:1397-1410.
159. Barha CK, Best JR, Rosano C, Yaffe K, Catov JM, Liu-Ambrose T. Sex-specific relationship between long-term maintenance of physical activity and cognition in the Health ABC Study: potential role of hippocampal and dorsolateral prefrontal cortex volume. *J Gerontol A Biol Sci Med Sci*. 2020;75:764-770.
160. Yaffe K, Lwi SJ, Hoang TD, et al. Military-related risk factors in female veterans and risk of dementia. *Neurology*. 2019;92:e205-e211.
161. Barnes DE, Byers AL, Gardner RC, Seal KH, Boscardin WJ, Yaffe K. Association of mild traumatic brain injury with and without loss of consciousness with dementia in US military veterans. *JAMA Neurol*. 2018;75:1055-1061.
162. Sugarman MA, McKee AC, Stein TD, et al. Failure to detect an association between self-reported traumatic brain injury and Alzheimer's disease neuropathology and dementia. *Alzheimers Dement*. 2019;15:686-698.
163. Plassman BL, Havlik RJ, Steffens DC, et al. Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. *Neurology*. 2000;55:1158-66.
164. Nordstrom A, Nordstrom P. Traumatic brain injury and the risk of dementia diagnosis: a nationwide cohort study. *PLoS Med*. 2018;15:e1002496.

165. Fann JR, Ribe AR, Pedersen HS, et al. Long-term risk of dementia among people with traumatic brain injury in Denmark: a Population-Based Observational Cohort Study. *Lancet Psychiatry*. 2018;5:424-431.
166. Morissette MP, Prior HJ, Tate RB, Wade J, Leiter JRS. Associations between concussion and risk of diagnosis of psychological and neurological disorders: a Retrospective Population-Based Cohort Study. *Fam Med Community Health* 2020;8:e000390.
167. Stubbs JL, Thornton AE, Sevick JM, et al. Traumatic brain injury in homeless and marginally housed individuals: a systematic review and meta-analysis. *Lancet Public Health*. 2020;5:e19-e32.
168. Mackelprang JL, Harpin SB, Grubenhoff JA, Rivara FP. Adverse outcomes among homeless adolescents and young adults who report a history of traumatic brain injury. *Am J Public Health*. 2014;104:1986-1992.
169. Liao CC, Chang HC, Yeh CC, Chou YC, Chiu WT, Chen TL. Socioeconomic deprivation and associated risk factors of traumatic brain injury in children. *J Trauma Acute Care Surg*. 2012;73:1327-1331.
170. Tani Y, Fujiwara T, Kondo K. Association between adverse childhood experiences and dementia in older Japanese adults. *JAMA Netw Open*. 2020;3:e1920740.
171. George KM, Lutsey PL, Kucharska-Newton A, et al. Life-course individual and neighborhood socioeconomic status and risk of cementia in the Atherosclerosis Risk in Communities Neurocognitive Study. *Am J Epidemiol*. 2020;189:1134-1142.
172. McMillan TM, Aslam H, Crowe E, Seddon E, Barry SJE. Associations between significant head injury and persisting disability and violent crime in women in prison in Scotland, UK: a cross-sectional study. *Lancet Psychiatry*. 2021;8:512-520.
173. Guinn AS, Ports KA, Ford DC, Breiding M, Merrick MT. Associations between adverse childhood experiences and acquired brain injury, including traumatic brain injuries, among adults: 2014 BRFSS North Carolina. *Inj Prev*. 2019;25:514-520.
174. Winstanley EL, Mahoney JJ, 3rd, Lander LR, et al. Something to despair: Gender differences in adverse childhood experiences among rural patients. *J Subst Abuse Treat*. 2020;116:108056.
175. Vlassoff C. Gender differences in determinants and consequences of health and illness. *J Health Popul Nutr*. 2007;25:47-61.
176. Hosseinpoor AR, Stewart Williams J, Amin A, et al. Social determinants of self-reported health in women and men: understanding the role of gender in population health. *PLoS One* 2012;7:e34799.
177. Adamson MM, Shakil S, Sultana T, et al. Brain injury and dementia in Pakistan: current perspectives. *Front Neurol*. 2020;11:299.
178. Zimmer Z, Fraser K, Grol-Prokopczyk H, Zajacova A. A global study of pain prevalence across 52 countries: examining the role of country-level contextual factors. *Pain*. 2021. https://doi.org/10.1097/j.pain.0000000000002557. Online ahead of print.
179. Elzahaf RA, Tashani OA, Unsworth BA, Johnson MI. The prevalence of chronic pain with an analysis of countries with a Human Development Index less than 0.9: a systematic review without meta-analysis. *Curr Med Res Opin*. 2012;28:1221-1229.
180. Whitlock EL, Diaz-Ramirez LG, Glymour MM, Boscardin WJ, Covinsky KE, Smith AK. Association between persistent pain and memory decline and dementia in a longitudinal cohort of elders. *JAMA Intern Med*. 2017;177:1146-1153.
181. Rong W, Zhang C, Zheng F, Xiao S, Yang Z, Xie W. Persistent moderate to severe pain and long-term cognitive decline. *Eur J Pain*. 2021;25:2065-2074.
182. Cao S, Fisher DW, Yu T, Dong H. The link between chronic pain and Alzheimer's disease. *J Neuroinflammation*. 2019;16:204.
183. Ikram M, Innes K, Sambamoorthi U. Association of osteoarthritis and pain with Alzheimer's diseases and related dementias among older adults in the United States. *Osteoarthr Cartil*. 2019;27:1470-1480.
184. Ezzati A, Wang C, Katz MJ, et al. The temporal relationship between pain intensity and pain interference and incident dementia. *Curr Alzheimer Res*. 2019;16:109-115.
185. Fillingim RB. Individual differences in pain: understanding the mosaic that makes pain personal. *Pain*. 2017;158(Suppl 1):S11-S18.
186. Fillingim RB. Sex, gender and pain. In: *Principles of Gender-Specific Medicine*. 3rd Edition, Legato M, eds. Academic Press; 2017:481-496.
187. Riley JL 3rd, Hastie BA, Glover TL, Fillingim RB, Staud R, Campbell CM. Cognitive-affective and somatic side effects of morphine and pentazocine: side-effect profiles in healthy adults. *Pain Med*. 2010;11:195-206.
188. Niesters M, Dahan A, Kest B, et al. Do sex differences exist in opioid analgesia? A systematic review and meta-analysis of human experimental and clinical studies. *Pain*. 2010;151:61-68.
189. Kumaradev S, Fayosse A, Dugravot A, et al. Timeline of pain before dementia diagnosis: a 27-year Follow-Up Study. *Pain*. 2021;162:1578-1585.
190. Dublin S, Walker RL, Gray SL, et al. Prescription opioids and risk of dementia or cognitive decline: a Prospective Cohort Study. *J Am Geriatr Soc*. 2015;63:1519-1526.
191. Landro NI, Fors EA, Vapenstad LL, Holthe O, Stiles TC, Borchgrevink PC. The extent of neurocognitive dysfunction in a multidisciplinary pain centre population. Is there a relation between reported and tested neuropsychological functioning? *Pain*. 2013;154:972-977.
192. Richards GC, Lluka LJ, Smith MT, et al. Effects of long-term opioid analgesics on cognitive performance and plasma cytokine concentrations in patients with chronic low back pain: a Cross-Sectional Pilot Study. *Pain Rep*. 2018;3:e669.
193. Schiltenwolf M, Akbar M, Hug A, et al. Evidence of specific cognitive deficits in patients with chronic low back pain under long-term substitution treatment of opioids. *Pain Physician*. 2014;17:9-20.
194. Knaul FM, Farmer PE, Krakauer EL, et al. Alleviating the access abyss in palliative care and pain relief-an imperative of universal health coverage: the Lancet Commission report. *Lancet*. 2018;391:1391-454.
195. Norman MA, Moore DJ, Taylor M, et al. Demographically corrected norms for African Americans and Caucasians on the Hopkins Verbal Learning Test-Revised, Brief Visuospatial Memory Test-Revised, Stroop Color and Word Test, and Wisconsin Card Sorting Test 64-Card Version. *J Clin Exp Neuropsychol*. 2011;33:793-804.
196. Kramer JH, Delis DC, Daniel M. Sex differences in verbal learning. *J Clin Psychol*. 1988;44:907-915.
197. Bleecker ML, Bolla-Wilson K, Agnew J, Meyers DA. Age-related sex differences in verbal memory. *J Clin Psychol*. 1988;44:403-411.
198. Herlitz A, Airaksinen E, Nordstrom E. Sex differences in episodic memory: the impact of verbal and visuospatial ability. *Neuropsychology*. 1999;13:590-597.
199. Siedlecki KL, Falzarano F, Salthouse TA. Examining gender differences in neurocognitive functioning across adulthood. *J Int Neuropsychol Soc*. 2019;25:1051-1060.
200. Vila-Castelar C, Fox-Fuller JT, Guzmán-Vélez E, Schoemaker D, Quiroz YT(2022) Advancing dementia research through a cultural approach: insights from work with Latinos in the U.S. and research call. *Nat Rev Neurol*. ePub ahead of print.
201. Brickman AM, Cabo R, Manly JJ. Ethical issues in cross-cultural neuropsychology. *Appl Neuropsychol*. 2006;13:91-100.
202. Flores I, Casaletto KB, Marquine MJ, et al. Performance of Hispanics and Non-Hispanic Whites on the NIH toolbox cognition battery: the roles of ethnicity and language backgrounds. *Clin Neuropsychol*. 2017;31:783-797.
203. Graves LV, Edmonds EC, Thomas KR, et al. Diagnostic accuracy and differential associations between ratings of functioning and neuropsychological performance in non-Hispanic Black and White older adults. *Clin Neuropsychol*. 2021;36(2):287-310.
204. Gauthier S, Rosa-Neto P, Morais JA, Webster C. *World Alzheimer Report 2021: Journey Through the Diagnosis of Dementia*. London: Alzheimer's Disease International; 2021.
205. Arce Renteria M, Vonk JMJ, Felix G, et al. Illiteracy, dementia risk, and cognitive trajectories among older adults with low education. *Neurology*. 2019;93:e2247-e2256.

206. Ardila A. Cross-cultural neuropsychology: history and prospects. *RUDN J Psychol Pedagogics*. 2020;17:64-78.
207. Nielsen TR, Jorgensen K. Cross-cultural dementia screening using the Rowland Universal Dementia Assessment Scale: a systematic review and meta-analysis. *Int Psychogeriatr*. 2020;32:1031-1044.
208. Ostrosky-Solis F, Ardila A, Rosselli M. NEUROPSI: a brief neuropsychological test battery in Spanish with norms by age and educational level. *J Int Neuropsychol Soc*. 1999;5:413-433.
209. Nitrini R, Bucki SMD, Yassuda MS, Fichman HC, Caramelli P. The Figure Memory Test: diagnosis of memory impairment in populations with heterogeneous educational background. *Dement Neuropsychol*. 2021;15:173-185.
210. Franzen S, van den Berg E, Goudsmit M, et al. A systematic review of neuropsychological tests for the assessment of dementia in non-western, low-educated or illiterate populations. *J Int Neuropsychol Soc*. 2020;26:331-351.
211. Sundermann EE, Barnes LL, Bondi MW, Bennett DA, Salmon DP, Maki PM. Improving detection of amnestic mild cognitive impairment with sex-specific cognitive norms. *J Alzheimers Dis*. 2021;84:1763-1770.
212. Stricker NH, Christianson TJ, Lundt ES, et al. Mayo normative studies: regression-based normative data for the Auditory Verbal Learning Test for ages 30-91 years and the importance of adjusting for sex. *J Int Neuropsychol Soc*. 2021;27:211-226.
213. Sundermann EE, Maki P, Biegon A, et al. Sex-specific norms for verbal memory tests may improve diagnostic accuracy of amnestic MCI. *Neurology*. 2019;93:e1881-e1889.
214. Angrisani M, Jain U, Lee J. Sex differences in cognitive health among older adults in India. *J Am Geriatr Soc*. 2020;68(Suppl 3):S20-S28.
215. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol*. 2012;11:1006-1012.
216. Cabeza R, Albert M, Belleville S, et al. Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. *Nat Rev Neurosci*. 2018;19:701-710.
217. Berlingeri M, Danelli L, Bottini G, Sberna M, Paulesu E. Reassessing the HAROLD model: is the hemispheric asymmetry reduction in older adults a special case of compensatory-related utilisation of neural circuits? *Exp Brain Res*. 2013;224:393-410.
218. Malpetti M, Ballarini T, Presotto L, et al. Gender differences in healthy aging and Alzheimer's dementia: a (18) F-FDG-PET study of brain and cognitive reserve. *Hum Brain Mapp*. 2017;38:4212-4227.
219. Jessen F, Amariglio RE, Buckley RF, et al. The characterisation of subjective cognitive decline. *Lancet Neurol*. 2020;19:271-278.
220. Gagnon M, Dartigues JF, Mazaux JM, et al. Self-reported memory complaints and memory performance in elderly French community residents: results of the PAQUID Research Program. *Neuroepidemiology*. 1994;13:145-154.
221. Peres K, Helmer C, Amieva H, et al. Gender differences in the prodromal signs of dementia: memory complaint and IADL-restriction. A prospective population-based cohort. *J Alzheimers Dis*. 2011;27:39-47.
222. Bassett SS, Folstein MF. Memory complaint, memory performance, and psychiatric diagnosis: a Community Study. *J Geriatr Psychiatry Neurol*. 1993;6:105-111.
223. Jonker C, Launer LJ, Hooijer C, Lindeboom J. Memory complaints and memory impairment in older individuals. *J Am Geriatr Soc*. 1996;44:44-49.
224. Sundermann EE, Edmonds EC, Delano-Wood L, et al. Sex influences the accuracy of subjective memory complaint reporting in older adults. *J Alzheimers Dis*. 2018;61:1163-1178.
225. Martinez JE, Pardilla-Delgado E, Guzman-Velez E, et al. Subjective cognitive decline and its relation to verbal memory and sex in cognitively unimpaired individuals from a Colombian cohort with autosomal-dominant Alzheimer's disease. *J Int Neuropsychol Soc*. 2021:1-9.
226. Magklara E, Stephan BCM, Robinson L. Current approaches to dementia screening and case finding in low- and middle-income countries: research update and recommendations. *Int J Geriatr Psychiatry*. 2019;34:3-7.
227. Dementia Research Group. Subjective memory deficits in people with and without dementia: findings from the 10/66 dementia research group pilot studies in low- and middle-income countries. *J Am Geriatr Soc*. 2009;57:2118-2124.
228. Jusot F, Grignon M, Dourgnon P. Access to psycho-social resources and health: exploratory findings from a survey of the French population. *Health Econ Policy Law*. 2008;3:365-391.
229. Barsky AJ, Peekna HM, Borus JF. Somatic symptom reporting in women and men. *J Gen Intern Med*. 2001;16:266-275.
230. Beekman AT, Copeland JR, Prince MJ. Review of community prevalence of depression in later life. *Br J Psychiatry*. 1999;174:307-311.
231. Steffens DC, Skoog I, Norton MC, et al. Prevalence of depression and its treatment in an elderly population: the Cache County study. *Arch Gen Psychiatry*. 2000;57:601-607.
232. Smith DJ, Kyle S, Forty L, et al. Differences in depressive symptom profile between males and females. *J Affect Disord*. 2008;108:279-284.
233. Edmonds EC, Delano-Wood L, Galasko DR, Salmon DP, Bondi MW, Alzheimer's Disease Neuroimaging I. Subjective cognitive complaints contribute to misdiagnosis of mild cognitive impairment. *J Int Neuropsychol Soc*. 2014;20:836-847.
234. Grambaite R, Hessen E, Auning E, Aarsland D, Selnes P, Fladby T. Correlates of subjective and mild cognitive impairment: depressive symptoms and CSF biomarkers. *Dement Geriatr Cogn Dis Extra*. 2013;3:291-300.
235. Lin KA, Choudhury KR, Rathakrishnan BG, et al. Marked gender differences in progression of mild cognitive impairment over 8 years. *Alzheimers Dement (N Y)*. 2015;1:103-110.
236. Cohen D, Eisdorfer C, Gorelick P, et al. Sex differences in the psychiatric manifestations of Alzheimer's disease. *J Am Geriatr Soc*. 1993;41:229-232.
237. Tao Y, Peters ME, Drye LT, et al. Sex differences in the neuropsychiatric symptoms of patients with Alzheimer's disease. *Am J Alzheimers Dis Other Demen*. 2018;33:450-457.
238. Bassiony MM, Steinberg MS, Warren A, Rosenblatt A, Baker AS, Lyketsos CG. Delusions and hallucinations in Alzheimer's disease: prevalence and clinical correlates. *Int J Geriatr Psychiatry*. 2000;15:99-107.
239. Hall JR, Wiechmann AR, Johnson LA, et al. The impact of APOE status on relationship of biomarkers of vascular risk and systemic inflammation to neuropsychiatric symptoms in Alzheimer's disease. *J Alzheimers Dis*. 2014;40:887-896.
240. Hollingworth P, Hamshere ML, Moskvina V, et al. Four components describe behavioral symptoms in 1,120 individuals with late-onset Alzheimer's disease. *J Am Geriatr Soc*. 2006;54:1348-1354.
241. Nagata T, Nakajima S, Shinagawa S, et al. Psychosocial or clinicodemographic factors related to neuropsychiatric symptoms in patients with Alzheimer's disease needing interventional treatment: analysis of the CATIE-AD study. *Int J Geriatr Psychiatry*. 2017;32:1264-1271.
242. Mega MS, Cummings JL, Fiorello T, Gornbein J. The spectrum of behavioral changes in Alzheimer's disease. *Neurology*. 1996;46:130-135.
243. Eikelboom WS, Pan M, Ossenkoppele R, al. e. Sex differences in neuropsychiatric symptoms in Alzheimer's disease dementia: a meta-analysis. *UNDER REVIEW*.
244. Jack CR, Jr., Wiste HJ, Weigand SD, et al. Age, sex, and APOE $\varepsilon 4$ effects on memory, brain structure, and β-amyloid across the adult life span. *JAMA Neurol*. 2015;72:511-519.

245. Buckley RF, Mormino EC, Rabin JS, et al. Sex differences in the association of global amyloid and regional tau deposition measured by positron emission tomography in clinically normal older adults. *JAMA Neurol*. 2019;76:542-551.
246. Hohman TJ, Dumitrescu L, Barnes LL, et al. Sex-specific association of apolipoprotein E with cerebrospinal fluid levels of tau. *JAMA Neurol*. 2018;75:989-998.
247. Altmann A, Tian L, Henderson VW, Greicius MD. Sex modifies the APOE-related risk of developing Alzheimer disease. *Ann Neurol*. 2014;75:563-573.
248. Oveisgharan S, Arvanitakis Z, Yu L, Farfel J, Schneider JA, Bennett DA. Sex differences in Alzheimer's disease and common neuropathologies of aging. *Acta Neuropathol*. 2018;136:887-900.
249. Sundermann EE, Maki PM, Rubin LH, et al. Female advantage in verbal memory: evidence of sex-specific cognitive reserve. *Neurology*. 2016;87:1916-1924.
250. Ossenkoppele R, Lyoo CH, Jester-Broms J, et al. Assessment of demographic, genetic, and imaging variables associated with brain resilience and cognitive resilience to pathological tau in patients with Alzheimer disease. *JAMA Neurol*. 2020;77:632-642.
251. Sundermann EE, Biegon A, Rubin LH, et al. Better verbal memory in women than men in MCI despite similar levels of hippocampal atrophy. *Neurology*. 2016;86:1368-1376.
252. Caldwell JZK, Berg JL, Cummings JL, Banks SJ, Alzheimer's Disease Neuroimaging I. Moderating effects of sex on the impact of diagnosis and amyloid positivity on verbal memory and hippocampal volume. *Alzheimers Res Ther*. 2017;9:72.
253. Caldwell JZK, Cummings JL, Banks SJ, Palmqvist S, Hansson O. Cognitively normal women with Alzheimer's disease proteinopathy show relative preservation of memory but not of hippocampal volume. *Alzheimers Res Ther*. 2019;11:109.
254. Sundermann EE, Maki PM, Reddy S, Bondi MW, Biegon A, Alzheimer's Disease Neuroimaging I. Women's higher brain metabolic rate compensates for early Alzheimer's pathology. *Alzheimers Dement (Amst)*. 2020;12:e12121.
255. Digma LA, Madsen JR, Rissman RA, et al. Women can bear a bigger burden: ante- and post-mortem evidence for reserve in the face of tau. *Brain Commun*. 2020;2:fcaa025.
256. Vila-Castelar C, Tariot PN, Sink KM, et al. Sex differences in cognitive resilience in preclinical autosomal-dominant Alzheimer's disease carriers and non-carriers: baseline findings from the API ADAD Colombia Trial. *Alzheimers Dement*. 2022;18(11):2272-2282. https://doi.org/10.1002/alz.12552. Online ahead of print.
257. Teunissen CE, Verberk IMW, Thijssen EH, et al. Blood-based biomarkers for Alzheimer's disease: towards clinical implementation. *Lancet Neurol*. 2022;21:66-77.
258. Mielke MM. Consideration of sex differences in the measurement and interpretation of Alzheimer disease-related biofluid-based biomarkers. *J Appl Lab Med*. 2020;5:158-169.
259. Mielke MM, Syrjanen JA, Blennow K, et al. Comparison of variables associated with cerebrospinal fluid neurofilament, total-tau, and neurogranin. *Alzheimers Dement*. 2019;15:1437-1447.
260. Bridel C, van Wieringen WN, Zetterberg H, et al. and the NFL Group. Diagnostic value of cerebrospinal fluid neurofilament light protein in neurology: a systematic review and meta-analysis. *JAMA Neurol*. 2019;76:1035-1048.
261. Hansson O, Lehmann S, Otto M, Zetterberg H, Lewczuk P. Advantages and disadvantages of the use of the CSF amyloid beta (Abeta) 42/40 ratio in the diagnosis of Alzheimer's Disease. *Alzheimers Res Ther*. 2019;11:34.
262. Bouter C, Vogelgsang J, Wiltfang J. Comparison between amyloid-PET and CSF amyloid-beta biomarkers in a clinical cohort with memory deficits. *Clin Chim Acta*. 2019;492:62-68.
263. Schoonenboom NS, Pijnenburg YA, Mulder C, et al. Amyloid beta(1-42) and phosphorylated tau in CSF as markers for early-onset Alzheimer disease. *Neurology*. 2004;62:1580-1584.
264. Buckley RF, Mormino EC, Chhatwal J, et al. Associations between baseline amyloid, sex, and APOE on subsequent tau accumulation in cerebrospinal fluid. *Neurobiol Aging*. 2019;78:178-185.
265. Li G, Shofer JB, Petrie EC, et al. Cerebrospinal fluid biomarkers for Alzheimer's and vascular disease vary by age, gender, and APOE genotype in cognitively normal adults. *Alzheimers Res Ther*. 2017;9:48.
266. Mattsson N, Cullen NC, Andreasson U, Zetterberg H, Blennow K. Association between longitudinal plasma neurofilament light and neurodegeneration in patients with Alzheimer disease. *JAMA Neurol*. 2019;76:791-799.
267. Baldacci F, Lista S, Manca ML, et al. Age and sex impact plasma NFL and t-Tau trajectories in individuals with subjective memory complaints: a 3-year follow-up study. *Alzheimers Res Ther*. 2020;12:147.
268. Pase MP, Beiser AS, Himali JJ, et al. Assessment of plasma total tau level as a predictive biomarker for dementia and related endophenotypes. *JAMA Neurol*. 2019;76:598-606.
269. Syrjanen JA, Campbell MR, Algeciras-Schimnich A, et al. Associations of amyloid and neurodegeneration plasma biomarkers with comorbidities. *Alzheimers Dement*. 2021. Online ahead of print.
270. Mattsson N, Zetterberg H, Janelidze S, et al. Plasma tau in Alzheimer disease. *Neurology*. 2016;87:1827-1835.
271. Dage JL, Wennberg AM, Airey DC, et al. Levels of tau protein in plasma are associated with neurodegeneration and cognitive function in a population-based elderly cohort. *Alzheimers Dement*. 2016;12:1226-1234.
272. Vergallo A, Megret L, Lista S, et al. Plasma amyloid beta 40/42 ratio predicts cerebral amyloidosis in cognitively normal individuals at risk for Alzheimer's disease. *Alzheimers Dement*. 2019;15:764-775.
273. Keshavan A, Pannee J, Karikari TK, et al. Population-based blood screening for preclinical Alzheimer's disease in a British birth cohort at age 70. *Brain*. 2021;144:434-449.
274. Brickman AM, Manly JJ, Honig LS, et al. Plasma p-tau181, p-tau217, and other blood-based Alzheimer's disease biomarkers in a multiethnic, community study. *Alzheimers Dement*. 2021;17:1353-1364.
275. Stephan BCM, Pakpahan E, Siervo M, et al. Prediction of dementia risk in low-income and middle-income countries (the 10/66 Study): an independent external validation of existing models. *Lancet Glob Health*. 2020;8:e524-e535.
276. Ferri CP, Jacob KS. Dementia in low-income and middle-income countries: different realities mandate tailored solutions. *PLoS Med*. 2017;14:e1002271.
277. World Health Organization on behalf of the United Nations Inter-Agency Working Group on Violence Against Women Estimation and Data. Violence Against Women Prevalence Estimates, 2018. *Global, Regional and National Prevalence Estimates for Intimate Partner Violence against Women and Global and Regional Prevalence Estimates for Non-partner Sexual Violence Against Women*. Geneva: World Health Organization; 2021.

How to cite this article: Mielke MM, Aggarwal NT, Vila-Castelar C, et al. Consideration of sex and gender in Alzheimer's disease and related disorders from a global perspective. *Alzheimer's Dement*. 2022;18:2707–2724. https://doi.org/10.1002/alz.12662