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The aging brain: risk factors and interventions for long term brain health in women

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Abstract

Purpose of review: Poor cognitive aging and dementia pose a significant public health burden, and women face unique risks compared to men. Recent research highlights the role of genetics, menopause, chronic disease, and lifestyle in risk and resilience in women's cognitive aging. This work suggests avenues for clinical action at midlife that may change the course of brain health in aging.

Recent findings: Studies indicate women's risk for poor cognitive aging relates in part to hormone changes at menopause, a time when memory, brain structure and function, and Alzheimer's pathology may be observed in women and not men. Medical and lifestyle risks including diabetes, hypertension, and low physical activity also contribute to women's unique risks. At the same time, literature on resilience suggests women may benefit from lifestyle and chronic disease intervention, possibly more than men. Current studies emphasize the importance of interacting genetic and lifestyle risks, and effects of social determinants of health.

Summary: Women have greater risk than men for poor cognitive aging; however, by treating the whole person, including genetics, lifestyle, and social environment, clinicians have an opportunity to support healthy cognitive aging in women and reduce the future public health burden of dementia.

Keywords

brain; lifestyle; memory; aging; hormones; menopause; cognition

Introduction

Women's brain health represents a major public health issue, with studies revealing sex differences in risk factors for poor cognitive aging, including Alzheimer's disease (AD). The National Institutes of Health also champions sex as a critical variable for research

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on risks and interventions in aging. Unfortunately, work in this space has lagged, in part due to implicit sex- and gender-bias. For example, women and female animals have historically been excluded from, or not considered fully in, brain aging-relevant research. Recent reviews show only 12.5% of randomized clinical trials for AD drugs evaluate results specifically in women(1).

This research disparity impacts clinical care, as women are diagnosed with and treated for cognitive impairment similarly to men, despite differences in baseline memory and symptom course. This present review discusses the latest studies on women's risks and interventions for cognitive aging, including genetic, medical, lifestyle, and social factors. The review concludes with practical recommendations to support brain health in women.

Risk factors for poor cognitive aging in women

Women and men differ in cognitive aging and dementia risk. With respect to AD, the most common type of dementia, two-thirds of people living with AD are women(2). Women also have steeper rates of decline after diagnosis(3), and due to greater resistance to pathology and stronger verbal memory(4–6), women face difficulty obtaining early diagnosis(7,8).

Literature to date emphasizes women's multifactorial risks, including genetics, environment, and lifestyle. Moreover, studies indicate that risks once seen as due to behavior or choice—from diabetes to educational attainment, exercise, and diet—in part reflect social determinants of health (SDoH), qualities of our social environment that promote or harm lifetime health(9). Importantly, SDoH underlie what are often described as race- or ethnicity-based risks for poor cognitive aging(9). With these caveats, the past year has brought key advances in understanding individual and interactive contributions to women's brain health risks.

Apolipoprotein E ε4

The ε4 allele of Apolipoprotein E (APOE) is the most common genetic risk for late onset AD. Having one copy of the ε4 allele increases risk for developing AD as much as four times higher in women compared to men age 65–75(10). Amyloid plaques and tau tangles are two core pathologies involved in Alzheimer's disease (11). Amyloid accumulation begins up to two decades before memory symptom onset, and the most popular model of Alzheimer's disease proposes that amyloid precedes and potentiates excessive tau physphorylation and aggregation of tau-based neurofibrillary tangles (12,13). While neuroinflammation driven by microglia initially plays a role in clearance of these proteins, sustained microglial activation has a role in AD progression (14). Recent work on sex differences in AD highlights that APOE ε4 facilitates AD pathology, including amyloid(15), tau(16), and microglial expression changes(17) in a sex-dependent manner, most often favoring worse effects for women. The ε4 allele also may interact with other genetic risks(18) and lifestyle risks such as high body mass index (BMI) and low physical activity(19). However, relationships between risk factors are complex. For example, among women age 18–89 years old with ε4 and family history of AD, higher BMI was recently associated with more favorable brain aging, and physical activity had more beneficial brain aging effects in men with ε4, compared to women(19). Also surprising is recent work in

mouse models showing that while APOE ε4 impacts the female sex hormone estrogen, and also reduces memory performance, hippocampal dendritic spine density, synaptic protein levels, and estrogen receptor activity, all of these APOE ε4 effects were equivalent across sexes(20). Sex differences in clinical impact in humans remain to be tested.

Critically, most extant human work on APOE ε4 and sex effects has been conducted in predominantly non-Hispanic White (nHW), highly educated samples, limiting generalizability of results. Ongoing work in multiethnic cohorts indicates APOE ε4 effects on memory and AD risk may be less relevant in African Americans and American Indians(21–24).

Menopause

The average age of menopause coincides with initial amyloid pathology accumulation in the brains of individuals on the AD continuum, decades before symptom onset(25). During the menopause transition, verbal memory also decreases transiently(26), and early, surgically-induced menopause negatively impacts cognition and dementia risk(27). As such, the role of menopause in women's risk for poor brain aging remains of high interest.

Notable recent studies have identified candidate contributors to menopause-associated memory change, including changes in brain gray and white matter structure in memory-relevant regions, and reduction in levels of brain function as assessed by glucose metabolism, adenosine triphosphate production, and blood flow (28,29). Mosconi and colleagues showed that these changes are specific to endocrine aging, and are not observed in similarly-aged men. In addition, recovery in aspects of brain structure and metabolism post-menopause were linked to better post-menopause global cognition(28). In a separate study, Buckley and colleagues showed in a sample of 328 cognitively normal individuals at midlife (mean age = 57), that post-menopausal, but not pre-menopausal women had greater levels of tau protein than men, as assessed by tau-Positron Emission Tomography(30).

Among sex hormone changes at menopause, estrogen loss has garnered most attention. Up to date studies emphasize estrogen's role in supporting verbal memory(29,31), predominance of estrogen receptors in key memory-related brain regions such as the hippocampus(29,31), and estrogen downregulation of enzymes essential for beta-amyloid generation(32). Estrogen also may have a role in reducing tau-phosphorylation, though findings have been mixed(33). Estrogen additionally impacts metabolic and cardiovascular system processes, and these effects differ by sex(34), potentially paving the way for indirect effects of estrogen loss on cognitive decline.

Exactly which women are at greatest cognitive risk due to menopause-related changes remains unclear. Growing evidence suggests APOE ε4 status and cardiometabolic conditions confer risk for menopause-induced brain changes(35). Still, significant discrepancies exist, potentially due to sample differences in age, comorbid conditions, menopause symptoms, race, and ethnicity(29,31).

Medical and Lifestyle Risks

Research indicates up to 40% of current AD cases could have been prevented with lifestyle change(36). Modifiable risks for AD include low education, hearing loss, head injury, hypertension, alcohol use, obesity, smoking, depression, social isolation, physical inactivity, diabetes, and air pollution(36). Additional factors associated with poor cognitive aging include poor nutrition, sleep problems, low cognitive engagement, and stress(37–40).

Among modifiable risks, diabetes and cardiometabolic syndrome significantly increase AD risk in postmenopausal women(41), and prediabetes may preferentially impact executive function, language, and age of dementia onset in women compared to men(42). Although obesity is a modifiable risk, recent work suggests that waist-to-hip ratio better predicts premature brain aging in women as compared to BMI or percent body fat(34). Further nuance is needed when examining obesity and BMI change in women over sixty, who may have poorer cognitive outcomes with variable or declining BMI, results not seen in men(43). Frailty may contribute to this finding, as Ward and colleagues recently showed that frailty contributed to dementia risk in midlife individuals beyond the effects of genetics, and frailty mediated the effects of healthy lifestyle behaviors on dementia risk(44). Finally, studies in women emphasize low education, hypertension, diabetes, and physical inactivity, as well as additional factors including stroke, not cohabitating, insomnia, and sleep apnea as linked to poorer cognition and dementia risk in midlife and aging(45,46).

In contrast to low education as a risk for AD, greater education builds cognitive reserve(47,48), which in theory can be a source of resilience in the face of cognitive aging. As noted earlier in this review, women face difficulty with early diagnosis of cognitive problems due to time-limited and sex-specific memory resilience (4–6)·(49). This memory resilience is present in women with type 2 diabetes and overweight/obesity(50), as well as in early onset and autosomal-dominant forms of AD(51), and may be based on differences in brain structure and function(4–6)·(52), or neurochemistry, such as greater levels of memory- and plasticity-supporting brain derived neurotrophic factor (BDNF) in aging women(32). However, this resilience is lost as AD progresses, and in a recent study of more than 20,000 aging women, has been shown to be lost in women who have more than one modifiable risk factor such as physical inactivity, or in those who are APOE ε4 carriers(50,53).

Low education is also among the SDoH mentioned above, meaning that education as an indicator of cognitive reserve may be better conceptualized as socially influenced rather than individualistic. In one recent study, lower education and income explained 50% of the difference in cognitive scores between nHW and non-Hispanic Black (nHB) or Hispanic older adults(54). Separate work has shown that socioeconomic status, diet, and physical activity mediated cognitive issues and all-cause dementia in nHB vs. nHW women(21). Moreover, factors such as acculturation(55), blood-based measurements such as insulin and glucagon(55), and rurality(56), may be particularly important for predicting cognitive outcomes in Mexican Americans and Mexican citizens, respectively. Recent work suggests that modifiable risks—and in particular diabetes, hypertension, and obesity—may explain more current cases of AD in nHB and Hispanic individuals as compared to nHW individuals, emphasizing potential power of interventions for risks impacted by SDoH(57).

Understanding modifiable risks most relevant by race and ethnicity may also help to target the most impactful interventions to specific individuals and communities(58).

Beyond these factors, women may be vulnerable to biopsychosocial risks, such as exposure to stressful events and effects of inflammation, when compared to men(59). In addition, social isolation, ageism, and self-beliefs about age may impact cognitive decline interactively in women(60). Although late-life depression is a modifiable risk(36), depression across the life course is also detrimental to brain structure in aging(61). As with other risks, biopsychosocial variables may differ in impact across race and ethnicity. For example, chronic inflammation may be critical for cognitive change over time in nHB adults(62), but less relevant in Mexican Americans(55), and neighborhood segregation and discrimination may impact memory, language, dementia risk, and brain structure in nHB individuals(63,64).

Interventions to support brain health in women

Despite increased risk factors facing women, recent literature highlights the power of medical care at midlife and positive health behaviors to support brain health into old age. Menopausal hormone therapy (MHT), and interventions for sleep, exercise, nutrition, cognitive activity, and stress hold promise. Findings in this literature often vary by sex, race, ethnicity, and APOE E4 status, underscoring the need for further work to enable precision medicine approaches.

Hormone Replacement Therapy

Given potential impact of menopause on women's long term brain health, menopausal hormone therapy (MHT) is a topic of ongoing interest. Unfortunately, it is also controversial. In brief, the Women's Health Initiative (WHI) and subsequent WHI sub-studies first showed that MHT increased risk for negative outcomes including cardiovascular disease, all-cause dementia, AD, and death, particularly when initiated after menopause(65). With that major caveat, the present literature supports long term cognitive benefit of MHT in women with early (i.e., prior to age 44) menopause(66), and has lent growing support for positive, long-term effects of MHT on cognition if initiated in typical-age menopause transition (i.e., in the "window of opportunity")(31).

As with work on menopause-related risks for cognitive decline, there are discrepancies among human clinical trials versus observational studies of MHT on cognitive outcomes, as well as differences when comparing human and animal model literature, regarding what genetic and medical risks might define women who benefit most from MHT, what treatment should be given, and for how long(29–31). Regarding who to treat, age, APOE ε4 status, and medical and lifestyle risks(29) are important to consider. At the same time, defining a risk is not always straightforward. For example, when considering APOE ε4 status, prior work supports carrying ε4 as an indicator for MHT brain-based benefit(67), yet separate studies show two copies may predict lack of MHT benefit(68), or even add risk(69). Furthermore, in typical practice, risks such as APOE ε4 status are unknown.

Beyond who to treat, another key question is what treatment to give. Targeting new estrogens or compounds that promote estrogen action is one avenue, with trials ongoing. Further, recent work has identified androgens(33) and FSH(70) as important. The latter proposal comes from rodent models, in which researchers found that FSH blockade reduced amyloid and tau accumulation and improved memory in female ovariectomized rodents, and reduced amyloid and tau accumulation similarly in male rodent models of AD(70).

Currently, MHT is not recommended for AD prevention or cognition preservation in women of menopausal age; rather, a personalized approach with consideration of key factors including age, menopausal stage, comorbidities and symptoms is warranted. Longitudinal studies are needed to further explore the association between cumulative estrogen exposure and cognitive function in later life.

A final note on MHT is that little is known of the impact of gender-affirming hormone therapy (GHT) on long-term cognitive health. GHT includes hormones taken at any point in the lifespan to align hormone levels with gender identity. The only recent study of GHT and cognition showed that older transgender women who received GHT for at least 10 years had lower memory scores than cisgender women, but similar scores to cisgender men(71). GHT, as with MHT, may have indirect impact on cognition through effects on cardiovascular and cerebrovascular health in transgender women in particular(72). Attention to potential GHT risks and benefits to cognitive aging is an ethical imperative, and continued lack of attention may exacerbate health disparities in transgender individuals(73) and exacerbate public health burden.

Medical and Lifestyle interventions

Recent findings emphasize the importance of exercise, nutrition, cognitive activity, stress, and psychological health for women's long term brain health. Two recent multidomain studies describe sex effects within lifestyle change and cognitive aging. First, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) showed no sex differences in effects of combined nutrition, exercise, cognitive training, and medical management on cognition in older adults(45). In contrast, clinical multidomain AD prevention including nutrition, exercise, stress management, sleep, and medical management in older adults showed stronger positive effects on atherosclerosis risk for cognitively normal women, and more positive effects on dementia risk scores in women with mild cognitive impairment or mild AD(74).

With respect to exercise, recent work has emphasized myokines and exerkines—signaling molecules, including hormones, metabolites, proteins, and acids, which are released by acute and chronic exercise(75,76). Exercise increases BDNF(77), including in the presence of ovariectomy(78), and increases peripheral and hippocampal irisin(75,79,80), which has a role in cardiovascular disease(81). Both irisin and exercise may mediate cognitive function(82,83), including in AD(80). The effects of exercise associated with pro- and anti-inflammatory cytokines are not fully understood and may depend on what organ releases the cytokine(81). Overall, impact of exercise on memory and brain function is clear, but mechanisms require further investigation(84).

As with other interventions, exercise effects may vary by sex, medical conditions including hypertension, and SDoH. In particular, exercise may impact amyloid burden more in men(15), and more positively change hippocampal blood flow in individuals with hypertension who are APOE ε4 carriers(85). Prevalence of physical inactivity, and importance of this factor for long term cognitive outcomes may also vary by geographical region and culture, and this difference may in turn have implications for where exercise interventions have most impact(57,86).

Women may benefit more than men from cognitive reserve(87), though educational attainment has been linked to less cognitive reserve effect in Black vs. nHW individuals across sexes(88). Larger and diverse social networks may promote cognitive reserve(89), and aging nHB individuals may face SDoH-related barriers to social interaction levels(90). In contrast, having a strong sense of purpose in life may delay dementia diagnosis(91), and may be an additional source of resilience in the face of dementia-related brain changes.

Regarding biopsychosocial risks, a recent 4-week, app-based stress intervention showed improvement in well-being, self-compassion, loneliness, and psychological distress in just several minutes per day in educators, the majority of whom were women, during the early Covid-19 pandemic(92). Finally, recent work suggests that health coaching improved quality of life and depression symptoms in post-and peri-menopausal women(93).

Current directions for clinical intervention

Clinical care, and in particular innovative and team-based care models that include women's health and brain health physicians and other health care providers in cooperation, can positively change women's knowledge of and motivation to support their own brain health and aging. Perhaps most powerful is the ability of clinicians to counter prevalent stigma by opening conversations with women about their family history of AD. In addition, women's health clinicians can take the following specific actions to support women's cognitive aging:

1. Have open discussions about menopausal effects on memory, and include the context of family or genetic risks for dementia when considering MHT;
2. Promote growth mindset, learning and cognitive challenge as part of healthy aging;
3. Improve early detection of cognitive deficits in women by having a lower threshold for recommending follow-up for subjective memory or cognitive concerns;
4. Encourage women to proactively communicate with primary care and other specialists to monitor and treat medical risks for poor brain aging, including diabetes, obesity, hypertension, depression and hearing loss;
5. Frame behaviors like exercise and healthy diet, quitting smoking, reducing alcohol, and improving sleep as ways to support current and long term brain health as well as reduce dementia risks;

6. Ask about, and consider intervening on, SDoH, including management of chronic stressors, rather than focusing on race and ethnicity as categorically linked to health outcomes;
7. Include supplementary assessments, such as waist-to-hip ratio, when using BMI to facilitate decision-making;
8. Provide culturally competent care and remove barriers to timely access and treatment of cognitive decline and dementia; and
9. Promote cognitive health equity through scalable community partnerships, learning collaboratives and innovative systems of care such as shared medicine appointments.

Conclusion

Addressing women's greater risk for poor cognitive aging must be a public health priority. Similarly, addressing SDoH that contribute to women's risk and underlie risks formerly attributed to race or ethnicity, is imperative. Additional work is needed regarding understanding the mechanisms behind women's risks and optimizing interventions for women. Optimizing women's health from the perspective of population health will take time, cooperation at multiple levels of society, and policy change. At the same time, there are practical steps clinicians can take now to increase odds that their women patients will thrive as they age.

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Key Points

Women's risks for poor brain aging include those similar to men's as well as unique risks.

Interventions to support healthy brain aging in women must consider risks for disease as well as the broader context of women's health.

Women may need more stringent memory and medical screening, lifestyle medicine support, and education about menopause as a risk factor for dementia.

Social determinants of health contribute to medical and lifestyle risks formerly conceptualized as based on race and ethnicity.

Data on some interventions, such as menopausal hormone therapy, remains incomplete, though important advances have been made.