HHS Public Access

Author manuscript

Curr Neurol Neurosci Rep. Author manuscript; available in PMC 2022 July 06.

Published in final edited form as:

Curr Neurol Neurosci Rep. ; 21(9): 46. doi:10.1007/s11910-021-01133-y.

A Lifecourse Perspective on Female Sex-Specific Risk Factors for Later Life Cognition

Amalia Peterson, MD,

Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, USA

Sarah E Tom, PhD, MPH

Department of Neurology, College of Physicians and Surgeons, Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA

Abstract

a) Purpose of review: The prevalence of Alzheimer's Disease and Related Dementias is greater in women compared to men. We provide a review of female sex-specific risk factors across the lifecourse for cognition in older adulthood, highlighting areas that need further study.

b) Recent findings: Pregnancy may affect late-life cognition, with adverse pregnancy outcomes associated with an increased risk of cognitive decline, but parity providing a protective effect. Cumulative estrogen exposure, influenced by age of menarche, menopause, and exogenous estrogen use, may modify a woman's risk for dementia. Menopause transition-associated symptoms may impact cognitive health at the time of the symptoms, but long-term effects remain unknown. As compared to natural menopause, surgical menopause seems to increase the risk for cognitive impairment.

c) Summary: Studies that have assessed the association between women's reproductive health and cognition have produced conflicting results. Future studies that address these inconsistencies among diverse populations are needed to better care for women throughout their lives.

Keywords

Alzheimer's disease; dementia; sex; women; risk factors; reproductive health

Introduction:

In 2019, people aged > 65 years comprised 9% of the global population, with a near doubling expected by 2050 (1). With global population aging, more people will live with

Corresponding Author: Amalia Peterson 622 W. 168th Street, New York, NY 10032. ajp2260@cumc.columbia.edu.

Human and Animal Rights: This article does not contain any studies with human or animal subjects performed by any of the authors.

Alzheimer's Disease and Related Dementias (ADRD). ADRD prevalence is greater in women compared to men, and this difference increases with age, across global regions (2). It is unclear whether this ADRD disparity relates to overall survival advantage, increased risk of developing ADRD, or longer survival with ADRD in women compared to men (3-5).

In this review, we will summarize female sex-specific risk factors for cognition, with a focus on human studies. We focus on knowledge gaps in [1] pregnancy history and long-term cognitive outcomes, [2] the significance of reproductive span and type of menopause on cognitive function, and [3] the impact of exogenous estrogen therapy on cognition. With better understanding of these sex-specific risk factors comes the possibility of risk reduction, with improved care and treatment for women throughout their lives.

Sex and Gender

Both sex and gender contribute to ADRD risk factors. In this review, sex refers to biological and physiological differences resulting from differences in sex chromosomes and gonadal hormones (3, 6). Sex-specific experiences across the female lifecourse include menarche, pregnancy and childbirth, and menopause. By contrast, gender refers to differences in environmental, social, and cultural influences (3, 6). These risk factors can occur in both men and women but are more commonly associated with certain gender identities. Examples of these differences include access to education and role as caregivers. Prior reviews of ADRD risk have addressed gender differences (3, 7). This review focuses on the rapidly expanding field of sex-specific women's reproductive health exposures and cognitive outcomes in older adulthood, incorporating a lifecourse approach (Table 1).

Adverse Pregnancy Outcomes

Pregnancy can be considered an acute physiologic stress test that may unmask underlying propensities for, or that may contribute to, maternal vascular response (8). Adverse pregnancy outcomes (APOs) may reflect the body's inability to meet the demands of pregnancy and include preeclampsia, gestational hypertension, fetal growth restriction, stillbirth, preterm birth (birth < 37 weeks gestation), miscarriage, and gestational diabetes (9, 10). Women with a history of APOs are at greater risk for subsequent cardiovascular disease compared to women without a history of APOs (9-11). Subsequent vascular outcomes are hypothesized to be key mediators of the relationship between APOs and late-life cognition (8, 12, 13).

Studies have found mixed evidence for the relationship between APOs and subsequent maternal ADRD outcomes. Some studies showed relationships between hypertensive disorders of pregnancy (preeclampsia or gestational hypertension) and poor processing speed in older adulthood and poor working memory and verbal learning 15 years after pregnancy (14, 15). Other studies found no relationship between hypertensive disorders of pregnancy and cognition (8, 16). Women with a history of hypertensive pregnancy disorder had greater brain atrophy and higher white matter lesion volume (14). A modest association between APOs and ADRD onset in some studies appears to be related to vascular dementia

(13, 17). Other studies found no relationships between hypertensive disorders of pregnancy and dementia onset (12, 18).

Limitations in this literature include use of recalled APOs and dementia diagnosis from medical registries (8, 12, 13, 16). Both strategies may misclassify respondents. As several studies have included respondents that may have been too young to experience age-related cognitive decline, longer follow-up as well as the linkage of prospectively collected APO data to cognition data from older adulthood are warranted (8, 12, 13, 16-18).

Pregnancy history

Pregnancy may benefit the aging brain through hormones, including increased progesterone and estrogen, the specific profile of estrogen, or immune function (19-22). Few studies consider gravidity and subsequent ADRD outcomes. One notable exception found a benefit in the number of first trimesters, but not third trimesters, on lower maternal ADRD risk. These results suggest an immune function benefit, which is strongest early in pregnancy (22). Another study further supported a protective effect of pregnancy, finding that the number of incomplete pregnancies, independent of parity, was related to lower maternal ADRD (23). A larger set of studies considers parity and ADRD outcomes. Some studies show that parous women have better cognition compared to nulliparous women. Other studies show that parity of 2 children is associated with higher cognition in older women, compared to parity of 0-1 or ≥ 3 children (12, 24-26). Overall, studies have not found a relationship between parity and cognitive decline. One study found that parity of ≥ 5 births is associated with reduced brain volume, but not Aβ deposition, Aβ positivity, or white matter hyperintensities in older, non-demented women (27). Such results do not fully support the hypotheses regarding hormonal and immunological pregnancy benefits. Gravidity and parity may reflect influences of pregnancy as well as parenting on the aging brain. Aspects of parenting related to older adult cognition, including frequency and the nature of interactions with children may reflect gender as well as sex differences (24, 28). Studies that have examined the role of parity and age at first birth on cognition in both men and women have found a similar relationship between parity for men and women but a cognitive advantage for age at first birth only among mothers (24, 28). Future studies including reasons for incomplete pregnancy and considering parity in both men and women may further illuminate pregnancy versus parenting influences on ADRD outcomes in women.

Estrogen Exposure:

Cumulative estrogen exposure has been proposed to modify a woman's risk of dementia. Estrogen exposure is primarily determined by the endogenous exposure of a woman's reproductive span, from menarche to menopause, but can be influenced by other aspects of reproductive history and use of exogenous estrogen-containing therapies, including oral contraceptive pills (OCPs) and hormone therapy (HT). As such, studies have considered reproductive history as an indirect indicator of estrogen exposure.

Endogenous Estrogen Exposure:

Age of Menarche:

Menarche is the first menstrual cycle, which, in US women, occurs between ages 12-13 on average (29). The few studies that have assessed the association between age of menarche and cognition have produced discrepant results. Women with older age of menarche may have an increased risk of dementia or mild cognitive impairment (30-32). When specific cognitive domains were assessed, visual memory and psychomotor speed were impaired but not verbal memory or executive function (33, 34). Still other studies, in geographically diverse groups of women, have found no association (19, 35-37). In the US, the average age of menarche has declined over time, from 13.3 years in women born before 1920 to 12.4 years in women born in the 1980s, which has been attributed to improved nutrition and increased weight (29, 38). Future studies are needed to determine whether the association between age of menarche and late-life cognition is confounded by social determinants of health, such as early-life nutrition, and whether the association is different in women in later birth cohorts.

Age of Menopause:

Natural menopause is the cessation of menses for at least 12 months in the absence of a medical or surgical cause, and occurs at an average age of 51 in women in the US (39, 40). Studies of the association between age of menopause and cognition are mixed. In one cohort, later age at natural menopause was associated with better verbal memory but not processing speed (41). Earlier menopause has been associated with worse Mini Mental Status Exam (MMSE) scores and an increased risk of dementia (30, 31, 37, 42). However, in some of these studies, the effects on verbal memory and MMSE score were small and of unclear clinical significance (41, 42). Others have found that later menopause is associated with an increased risk of dementia after age 75 (19). Some studies have found no association between age of menopause and cognitive function (32, 35, 36). Not all studies have differentiated type of menopause or accounted for other sources of estrogen exposure. Future studies that include these measures are warranted to help clarify the effect of age of menopause on cognition.

Reproductive Span:

The reproductive span is the interval between age of menarche and menopause. As a risk factor, it may relate to cognitive decline separate from those events individually, as several studies have found differences in cognition associated with age of menarche or menopause and reproductive span (34, 43). One prospective longitudinal study found that longer reproductive span was associated with higher late-life global cognition, but did not assess dementia directly (44). In a separate study, longer reproductive span was associated with an increased risk of Alzheimer’s disease (AD) in people with at least one APOE4 allele (45). While other studies have failed to replicate the association with APOE4, some also found an increased risk of AD in women who had longer reproductive spans (19). Others have found the opposite, with a shorter reproductive span being associated with an increased risk of dementia (30, 31). Furthermore, not all studies have found an association between reproductive span and dementia incidence (35). Studies variably include other factors that

affect lifetime estrogen exposure beyond reproductive span. Including factors such as parity, menopausal type, and exogenous estrogen use may help to clarify the effect of reproductive span on cognition in future studies.

Exogenous Estrogen Exposure:

OCP Use:

First approved by the FDA as a contraceptive in 1960, OCPs are now one of the most common forms of contraception, with more than 80% of women using them at some time in their life (46). Most OCPs are a combined formulation of estrogen and a progestin, with formulations differing in the type of hormones, the dose, and the amount of hormone delivered across the cycle (47). OCP use may have a beneficial effect on cognition, though studies are equivocal. Some studies have found a positive effect of OCP use on global cognition or particular subdomains, including executive function, visuospatial ability, and verbal memory (33, 37, 48, 49). Still others have found no association with cognitive impairment (34, 42, 50, 51). Future studies that consider the type of OCP used, the timing of initiation, and duration of use are needed to better understand the effect of OCP use on cognition.

Hormone Therapy:

HT encompasses estrogen and estrogen-progestogen therapies and has four FDA approved indications: [1] bothersome vasomotor symptoms (VMS), [2] prevention of bone loss, [3] hypoestrogenism caused by hypogonadism castration or primary ovarian insufficiency, and [4] genitourinary symptoms (52). Progestogen is prescribed in combination with estrogen in women with uteruses to reduce the risk of endometrial cancer from unopposed estrogen. HT varies in type of estrogen, type of progestogen, dose, and route of administration.

Observational studies prior to the early 2000s showed that HT use was associated with a decreased risk of Alzheimer’s disease (53). The Women’s Health Initiative Memory Study (WHIMS), a randomized control trial (RCT), found that women who were randomized to receive estrogen and progestin had double the risk of all-cause dementia during a four year follow-up and women who received estrogen alone had a trend towards increased risk of dementia (54, 55). Although women in WHIMS were age 65 or older, prior to this study, 85% of women in the US who used HT did so within one year of their final period, at an average age of 52 (56, 57). As such, although this study led to changes in prescribing practices, it was criticized as not being generalizable to perimenopausal and younger postmenopausal women, the population which most frequently uses HT.

Studies since WHIMS have not found that same degree of risk. RCTs have found no increased risk of cognitive impairment in women treated within three years of their last period, when initiated between age 50-55, or whether initiated within six years of menopause compared to ten years, and found no increased long-term risk of death from AD (58-61). Two studies using national registry data have found an increased risk of AD among HT users, though one found an increased risk with duration of use of less than five years and

the other with more than ten years (62, 63). A third study found a reduced risk of death from vascular dementia and AD among HTs users treated for more than five years (64).

Among women who have undergone surgical menopause (uterus removal with one or both ovaries conserved, or ovary removal with or without uterus conservation, before the onset of natural menopause), HT use seems to have a positive effect on memory. Women who receive estrogen therapy after oophorectomy perform comparable to premenopausal controls on working memory tasks (65), and women treated with estrogen until at least age 50 following bilateral oophorectomy had no increased risk of cognitive impairment or dementia (66). Additionally, it has been shown that women who initiate HT within five years of surgical menopause and continue treatment for at least ten have less decline in cognition, including episodic memory, semantic memory, and visuospatial ability (67). Interestingly, in this cohort there was no association between HT use and Alzheimer's disease pathology, suggesting that HT use may provide a protective effect independent of pathological changes (67, 68). However, some imaging studies have found that HT users have more favorable biomarker profiles, with higher FDG uptake on PET imaging, trends towards reduced tau, and larger gray and white matter volume (69, 70). Future studies are needed to understand how HT, including duration and type of therapy, affect biomarkers and neuropathological changes.

There are two main hypotheses proposed to explain the difference in the effect of HT in observational studies and more recent RCTs, as compared to WHIMS. The critical window hypothesis suggests that the effects of HT depend on the timing of initiation of treatment with respect to age of menopause, with beneficial effects seen when started soon after menopause (57). The healthy cell hypothesis proposes that estrogen is beneficial if neurons are healthy at the time of exposure, but can be detrimental and exacerbate decline if they are not healthy (71).

A limitation to the RCTs is that women who participated were not required to have indications for HT use, and thus the effect of HT on cognition in women with significant VMS remains unknown. Although it appears that short term use of HT in younger women has no detrimental effect on women, the risk of long term use remains uncertain (56). A RCT in younger peri- and postmenopausal women with indications for HT with long-term follow-up is needed to answer this question. Future observational studies must be mindful of the age of initiation of treatment, duration, and formulation of HT used.

Selective Estrogen Receptor Modulators:

Selective estrogen receptor modulators (SERMs) act as either estrogen receptor agonists or antagonists, depending on the targeted tissue, and can be used to treat breast cancer and osteoporosis. Studies of the effects of SERMs on cognition are mixed. While one RCT found that postmenopausal women taking raloxifene had a reduced risk of developing MCI but not AD, a recent retrospective study of women with breast cancer found no association with dementia risk (72, 73). A pilot RCT found no cognitive effect of raloxifene in women with AD (74). Tibolone, available in Asia and Europe but not the US, may increase the risk of dementia, though this is not a consistent finding (63, 75). The effect of SERMs on cognition may depend on the type of SERM used.

Menopausal Symptoms:

The majority of women in the United States experience menopause transition-associated symptoms (76). Common symptoms include VMS (hot flashes and night sweats), sleep disturbance, mood changes, and cognitive disturbances (76). Symptoms often begin in perimenopause, when hormone levels fluctuate (76). Menopausal women are thought to have a narrowed thermoneutral zone, with slight increases in core body temperature triggering peripheral vasodilation and sweating (76, 77).

In addition to having a negative impact on quality of life, symptoms seem to impact cognitive health as well. The frequency and severity of hot flashes are associated with subjective cognitive complaints during menopause (78). This may extend to objective deficits in verbal memory and processing speed, but studies are inconsistent (79-82). A subset of studies have found a consistent association between physiological hot flashes measured via skin conductance, but not subjective hot flashes, and impaired verbal memory (83, 84). This may be because physiologically measured hot flashes are not subject to factors that influence perception and recall (85).

Although much work has been done focusing on VMS, other menopausal symptoms may also be associated with cognition. Depression and anxiety during menopause predict worse verbal memory, executive function, and processing speed (80, 81, 86). While there may be a relationship between sleep and cognitive deficits, not all studies have found an association (81, 83).

The cascade hypothesis posits that VMS lead to sleep disturbances, which in turn lead to memory decline (83, 87). However, hot flashes remain a significant predictor of cognitive impairment after adjusting for sleep parameters (83). The cognitive changes in women with VMS could be the result of cerebrovascular injury, as VMS are also associated with cardiovascular disease risk factors and clinical events (88, 89). More physiologically-measured hot flashes during sleep are associated with greater white matter hyperintensity burden among midlife women without clinical cardiovascular disease (90). Additionally, peri- and postmenopausal women with greater waking after sleep onset had greater white matter disease burden, adjusting for cardiovascular risk factors and hot flashes (91). Thus, white matter disease could serve as a marker for risk of cognitive decline and dementia. Whether VMS are associated with changes in AD biomarkers needs to be studied.

Most studies have sought to determine the effect of VMS on cognition in cross-sectional designs, with a focus on the period of the menopausal transition, when the overall risk for dementia is low. As such, studies typically examine cognitive subdomains. An exception found that women with the most severe overall symptomatology experienced global cognitive deficits, reflected in worse MMSE scores (79). Although one study found that perimenopausal cognitive deficits resolve post-menopause, more longitudinal studies with sufficiently long follow-up are needed to understand the long-term cognitive trajectories of women with a high burden of menopausal symptoms (92).

Surgical Menopause:

Although a distinction between uterus removal with one or both ovaries conserved versus ovary removal with or without uterus conservation is not always made, the hormonal changes are distinct (40, 93). Women who undergo natural menopause experience fluctuations and a gradual decline in hormone levels (40). In contrast, bilateral oophorectomies lead to an abrupt drop in estrogen and progesterone levels. Hysterectomies are also thought to affect hormone levels, when performed in isolation, by causing decreased blood supply to the ovaries, thereby leading to hormonal dysregulation (94, 95).

Surgical menopause is associated with long-term health risks, including cardiovascular disease, poor bone health, and mood disturbances (96, 97). This seems to extend to increased risk of cognitive decline and dementia as well. Most studies, though not all, have found that surgical menopause has a negative impact on cognition (41, 42, 98, 99). Women who have undergone surgical menopause have been shown to have worse semantic, verbal, visual, and working memory, as well as faster decline in global cognition, episodic memory, and semantic memory (65, 67, 100). Women who have undergone oophorectomy have a nearly doubled risk of cognitive impairment or dementia, and the risk is increased with younger age of surgery (66). Hysterectomies have been associated with an increased risk of early-onset dementia, and this risk was increased in younger women and women who also had an oophorectomy (101). Others have found an increased risk of dementia in women who had undergone hysterectomy prior to natural menopause, regardless of age at surgery (31). In a study that did not differentiate between type of surgery, women with an earlier age at surgical menopause had faster cognitive decline and increased AD neuropathology (67).

The underlying cause for this increased risk of impaired cognition remains unclear. Evidence of a benefit of HT immediately following surgery suggests that the abrupt reduction in estrogen may mediate this association, but this remains a controversial topic (see HT section). Although reduction in estrogen following surgical menopause may play a role, this would not fully account for the effect seen in women who have undergone hysterectomies alone or unilateral oophorectomies. Women seem to have an increased risk of cognitive decline, regardless of etiology, when menopause occurs before age 40 (102). However, surgical menopause cannot solely be considered as a proxy for reproductive span, as women with the same reproductive span who had gone through natural menopause do not have an increased risk of AD related pathology (67).

Few studies consider the underlying pathology causing these changes. Imaging studies have found that women who have undergone bilateral oophorectomy have medial temporal lobe atrophy on imaging, while women who have had a hysterectomy showed no difference in gray or white matter volume, but reduced FDG-PET uptake (70, 103). Surgical menopause is associated with increased AD-related pathology, and this finding seems to be driven by women who were younger at time of surgery (67, 68). Given the association between surgical menopause and cardiovascular disease, it is also possible that cognitive changes are due to vascular pathways. Studies to determine whether surgical menopause is associated with other types of neuropathologies are warranted. Future studies would benefit from distinguishing type of surgical menopause, to account for the distinct hormonal changes

associated with each, and longer follow-up, to avoid participants that are too young to experience age-related cognitive decline.

Future Directions:

Moving forward, to better understand the role of sex-specific risk factors for ADRD, we must consider what groups of women are being studied (Table 2). Over the 20th century, there have been changes in OCP and HT use, as well as gravidity and parity. Social determinants of health (SDOH) across the life course have influenced women's reproductive health and cognitive aging (104, 105). Given these shifts, findings from studies of women born in the early 1900s may not be applicable to baby boomers and later birth cohorts, and these younger populations of women should be studied as they age. There is also a need to study sex-differences in underrepresented populations. Some transgender individuals use gender-affirming hormone therapy (GAHT). While there is evidence that GAHT can improve quality of life and mental health, there is no data on the long-term effects of GAHT on late-life cognition, and findings from studies of HT in cisgender women cannot be easily extrapolated to transgender women (106). Most research on sex risk factors has been done in primarily non-Hispanic white samples, and few studies have examined whether there are racial or ethnic differences (107). One notable exception found no effect on cognition with respect to race and age of menarche, menopause, reproductive span, or hysterectomy (31), but more studies are needed. Compared to whites, Hispanics and Blacks are more likely to have ADRD and are among the fastest growing racial/ethnic groups aged > 65 in the US (4). These changes underscore the need to understand the role of SDOH across the life course with respect to ADRD outcomes (104). Although there are studies that show independent associations between SDOH, women's reproductive health, and late-life cognition, it remains to be seen whether SDOH diminish or intensify the relationship between women's health and cognition.

Conclusions:

This review highlights what is known about female sex-specific risk factors for ADRD, and the ongoing need to characterize risk factors across the lifecourse. Adverse pregnancy outcomes may increase the risk of cognitive decline, while parity may provide a protective effect. Estrogen exposure over the lifecourse, influenced by endogenous and exogenous estrogen, may affect cognition, as well as type of menopause and menopause transition-associated symptoms. We note that, across various aspects of reproductive history, there are conflicting studies. The inconsistencies in these findings may be due to differences in other aspects of reproductive history across populations, adjustments for potential confounders, and study design, including length of follow-up. A better understanding of these sex-specific risk factors across the lifecourse among diverse populations offers the possibility of new treatment targets, and, ultimately, improved care.

References

1. United Nations, Department of Economic and Social Affairs, Population Division (2020). World Population Ageing 2019 (ST/ESA/SER.A/444).

2. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement. 2013;9(1):63–75.e2. [PubMed: 23305823]

3. Mielke MM, Vemuri P, Rocca WA. Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences. Clin Epidemiol. 2014;6:37–48. [PubMed: 24470773]

4. 2021 Alzheimer's disease facts and figures. Alzheimers Dement. 2021;17(3):327–406. [PubMed: 33756057]

5. Larson EB, Shadlen MF, Wang L, McCormick WC, Bowen JD, Teri L, et al.Survival after initial diagnosis of Alzheimer disease. Ann Intern Med. 2004;140(7):501–9. [PubMed: 15068977]

6. Ferretti MT, lulita MF, Cavedo E, Chiesa PA, Schumacher Dimech A, Santuccione Chadha A, et al.Sex differences in Alzheimer disease - the gateway to precision medicine. Nat Rev Neurol. 2018;14(8):457–69. [PubMed: 29985474]

7. Nebel RA, Aggarwal NT, Barnes LL, Gallagher A, Goldstein JM, Kantarci K, et al.Understanding the impact of sex and gender in Alzheimer's disease: A call to action. Alzheimers Dement. 2018;14(9):1171–83. [PubMed: 29907423] •This is a review of sex and gender differences in Alzheimer's disease

8. Dayan N, Kaur A, Elharram M, Rossi AM, Pilote L. Impact of Preeclampsia on Long-Term Cognitive Function. Hypertension. 2018;72(6):1374–80. [PubMed: 30571227]

9. Okoth K, Chandan JS, Marshall T, Thangaratinam S, Thomas GN, Nirantharakumar K, et al.Association between the reproductive health of young women and cardiovascular disease in later life: umbrella review. Bmj. 2020;371:m3502. [PubMed: 33028606] •An umbrella review of the association between reproductive history and risk of cardiovascular disease

10. Staff AC, Redman CW, Williams D, Leeson P, Moe K, Thilaganathan B, et al.Pregnancy and Long-Term Maternal Cardiovascular Health: Progress Through Harmonization of Research Cohorts and Biobanks. Hypertension. 2016;67(2):251–60. [PubMed: 26667417]

11. Lane-Cordova AD, Khan SS, Grobman WA, Greenland P, Shah SJ. Long-Term Cardiovascular Risks Associated With Adverse Pregnancy Outcomes: JACC Review Topic of the Week. J Am Coll Cardiol. 2019;73(16):2106–16. [PubMed: 31023435]

12. Nelander M, Cnattingius S, Åkerud H, Wikström J, Pedersen NL, Wikström AK. Pregnancy hypertensive disease and risk of dementia and cardiovascular disease in women aged 65 years or older: a cohort study. BMJ Open. 2016;6(1):e009880.

13. Basit S, Wohlfahrt J, Boyd HA. Pre-eclampsia and risk of dementia later in life: nationwide cohort study. Bmj. 2018;363:k4109. [PubMed: 30333106]

14. Mielke MM, Milic NM, Weissgerber TL, White WM, Kantarci K, Mosley TH, et al.Impaired Cognition and Brain Atrophy Decades After Hypertensive Pregnancy Disorders. Circ Cardiovasc Qual Outcomes. 2016;9(2 Suppl 1):S70–6. [PubMed: 26908863]

15. Adank MC, Hussainali RF, Oosterveer LC, Ikram MA, Steegers EAP, Miller EC, et al.Hypertensive Disorders of Pregnancy and Cognitive Impairment: A Prospective Cohort Study. Neurology. 2021;96(5):e709–e18. [PubMed: 33380500] •This study found an association between a history of hypertensive disorders of pregnancy and worse working memory and verbal learning 15 years after pregnancy

16. Harville EW, Guralnik J, Romero M, Bazzano LA. Reproductive History and Cognitive Aging: The Bogalusa Heart Study. Am J Geriatr Psychiatry. 2020;28(2):217–25. [PubMed: 31350162]

17. Andolf E, Bladh M, Möller L, Sydsjö G. Prior placental bed disorders and later dementia: a retrospective Swedish register-based cohort study. Bjog. 2020;127(9):1090–9. [PubMed: 32145044]

18. Andolf EG, Sydsjö 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(4):464–71. [PubMed: 28094840]

19. Najar J, Ostling S, Waern M, Zettergren A, Kern S, Wetterberg H, et al.Reproductive period and dementia: A 44-year longitudinal population study of Swedish women. Alzheimers Dement. 2020;16(8):1153–63. [PubMed: 32573980]

20. Singh MProgesterone-induced neuroprotection. Endocrine. 2006;29(2):271–4. [PubMed: 16785602]

21. Schock H, Zeleniuch-Jacquotte A, Lundin E, Grankvist K, Lakso H, Idahl A, et al.Hormone concentrations throughout uncomplicated pregnancies: a longitudinal study. BMC Pregnancy Childbirth. 2016;16(1):146. [PubMed: 27377060]
22. Fox M, Berzuini C, Knapp LA, Glynn LM. Women's Pregnancy Life History and Alzheimer's Risk: Can Immunoregulation Explain the Link?Am J Alzheimers Dis Other Demen. 2018;33(8):516–26. [PubMed: 30060670]
23. Jang H, Bae JB, Dardiotis E, Scarmeas N, Sachdev PS, Lipnicki DM, et al.Differential effects of completed and incomplete pregnancies on the risk of Alzheimer disease. Neurology. 2018;91(7):e643–e51. [PubMed: 30021919]
24. Read SL, Grundy EMD. Fertility History and Cognition in Later Life. J Gerontol B Psychol Sci Soc Sci. 2017;72(6):1021–31. [PubMed: 26926956]
25. Saenz JL, Díaz-Venegas C, Crimmins EM. Fertility History and Cognitive Function in Late Life: The Case of Mexico. J Gerontol B Psychol Sci Soc Sci. 2021;76(4):e140–e52. [PubMed: 31603514]
26. Grandi SM, Filion KB, Yoon S, Ayele HT, Doyle CM, Hutcheon JA, et al.Cardiovascular Disease-Related Morbidity and Mortality in Women With a History of Pregnancy Complications. Circulation. 2019;139(8):1069–79. [PubMed: 30779636]
27. Jung JH, Lee GW, Lee JH, Byun MS, Yi D, Jeon SY, et al.Multiparity, Brain Atrophy, and Cognitive Decline. Front Aging Neurosci. 2020;12:159. [PubMed: 32581769]
28. Bordone V, Weber D. Number of children and cognitive abilities in later life. Vienna Yearbook of Population Research. 2012;10:95–126.
29. McDowell MA, Brody DJ, Hughes JP. Has age at menarche changed? Results from the National Health and Nutrition Examination Survey (NHANES) 1999-2004. J Adolesc Health. 2007;40(3):227–31. [PubMed: 17321422]
30. Yoo JE, Shin DW, Han K, Kim D, Won HS, Lee J, et al.Female reproductive factors and the risk of dementia: a nationwide cohort study. Eur J Neurol. 2020;27(8):1448–58. [PubMed: 32396982]
31. Gilsanz P, Lee C, Corrada MM, Kawas CH, Quesenberry CP, Jr., Whitmer RA. Reproductive period and risk of dementia in a diverse cohort of health care members. Neurology. 2019;92(17):e2005–e14. [PubMed: 30923235] •This study found that reproductive history characteristics related to shorter exposure to endogenous estrogen are associated with an increased risk of dementia
32. Shimizu Y, Sawada N, Iwasaki M, Shikimoto R, Nozaki S, Mimura M, et al.Reproductive history and risk of cognitive impairment in Japanese women. Maturitas. 2019;128:22–8. [PubMed: 31561818]
33. Karim R, Dang H, Henderson VW, Hodis HN, St John J, Brinton RD, et al.Effect of Reproductive History and Exogenous Hormone Use on Cognitive Function in Mid- and Late Life. J Am Geriatr Soc. 2016;64(12):2448–56. [PubMed: 27996108]
34. Ryan J, Carriere I, Scali J, Ritchie K, Ancelin ML. Life-time estrogen exposure and cognitive functioning in later life. Psychoneuroendocrinology. 2009;34(2):287–98. [PubMed: 18947934]
35. Prince MJ, Acosta D, Guerra M, Huang Y, Jimenez-Velazquez IZ, Llibre Rodriguez JJ, et al.Reproductive period, endogenous estrogen exposure and dementia incidence among women in Latin America and China; A 10/66 population-based cohort study. PLoS One. 2018;13(2):e0192889. [PubMed: 29489847] •This study found no association between reproductive history characteristics related to endogenous estrogen exposure and dementia incidence
36. Fox M, Berzuini C, Knapp LA. Cumulative estrogen exposure, number of menstrual cycles, and Alzheimer's risk in a cohort of British women. Psychoneuroendocrinology. 2013;38(12):2973–82. [PubMed: 24064221]
37. Song X, Wu J, Zhou Y, Feng L, Yuan JM, Pan A, et al.Reproductive and hormonal factors and risk of cognitive impairment among Singapore Chinese women. Am J Obstet Gynecol. 2020;223(3):410 e1- e23. [PubMed: 32112728]
38. Butts SF, Seifer DB. Racial and ethnic differences in reproductive potential across the life cycle. Fertil Steril. 2010;93(3):681–90. [PubMed: 19939362]

39. Gold EB, Bromberger J, Crawford S, Samuels S, Greendale GA, Harlow SD, et al.Factors associated with age at natural menopause in a multiethnic sample of midlife women. Am J Epidemiol. 2001;153(9):865–74. [PubMed: 11323317]
40. Edwards H, Duchesne A, Au AS, Einstein G. The many menopauses: searching the cognitive research literature for menopause types. Menopause. 2019;26(1):45–65. [PubMed: 29994973] •This review highlights the importance of distinguishing type of menopause in studies of cognition
41. Kuh D, Cooper R, Moore A, Richards M, Hardy R. Age at menopause and lifetime cognition: Findings from a British birth cohort study. Neurology. 2018;90(19):e1673–e81. [PubMed: 29643079]
42. McLay RN, Maki PM, Lyketsos CG. Nulliparity and late menopause are associated with decreased cognitive decline. J Neuropsychiatry Clin Neurosci. 2003;15(2):161–7. [PubMed: 12724456]
43. Rasgon NL, Magnusson C, Johansson AL, Pedersen NL, Elman S, Gatz M. Endogenous and exogenous hormone exposure and risk of cognitive impairment in Swedish twins: a preliminary study. Psychoneuroendocrinology. 2005;30(6):558–67. [PubMed: 15808925]
44. Matyi JM, Rattinger GB, Schwartz S, Buhusi M, Tschanz JT. Lifetime estrogen exposure and cognition in late life: the Cache County Study. Menopause. 2019;26(12):1366–74. [PubMed: 31613825]
45. Geerlings Ml, Ruitenberg A, Witteman JC, van Swieten JC, Hofman A, van Duijn CM, et al.Reproductive period and risk of dementia in postmenopausal women. Jama. 2001;285(11):1475–81. [PubMed: 11255424]
46. Mosher WD, Martinez GM, Chandra A, Abma JC, Willson SJ. Use of contraception and use of family planning services in the United States: 1982–2002. Adv Data. 2004(350):1–36.
47. Beltz AM, Hampson E, Berenbaum SA. Oral contraceptives and cognition: A role for ethinyl estradiol. Horm Behav. 2015;74:209–17. [PubMed: 26122296]
48. Egan KR, Gleason CE. Longer duration of hormonal contraceptive use predicts better cognitive outcomes later in life. J Womens Health (Larchmt). 2012;21(12):1259–66. [PubMed: 22994984]
49. Li FD, He F, Chen TR, Xiao YY, Lin ST, Shen W, et al.Reproductive history and risk of cognitive impairment in elderly women: a cross-sectional study in eastern China. J Alzheimers Dis. 2016;49(1):139–47. [PubMed: 26444784]
50. Tierney MC, Ryan J, Ancelin ML, Moineddin R, Rankin S, Yao C, et al.Lifelong estrogen exposure and memory in older postmenopausal women. J Alzheimers Dis. 2013;34(3):601–8. [PubMed: 23246919]
51. Heys M, Jiang C, Cheng KK, Zhang W, Au Yeung SL, Lam TH, et al.Life long endogenous estrogen exposure and later adulthood cognitive function in a population of naturally postmenopausal women from Southern China: the Guangzhou Biobank Cohort Study. Psychoneuroendocrinology. 2011;36(6):864–73. [PubMed: 21185655]
52. The NHTPSAP. The 2017 hormone therapy position statement of The North American Menopause Society. Menopause. 2017;24(7):728–53. [PubMed: 28650869]
53. Yaffe K, Sawaya G, Lieberburg I, Grady D. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. Jama. 1998;279(9):688–95. [PubMed: 9496988]
54. Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, et al.Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. Jama. 2004;291(24):2947–58. [PubMed: 15213206]
55. Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, et al.Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. Jama. 2003;289(20):2651–62. [PubMed: 12771112]
56. Maki PM, Girard LM, Manson JE. Menopausal hormone therapy and cognition. BMJ. 2019;364:l877. [PubMed: 30842090]
57. Maki PM. Critical window hypothesis of hormone therapy and cognition: a scientific update on clinical studies. Menopause. 2013;20(6):695–709. [PubMed: 23715379]
58. Manson JE, Aragaki AK, Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, et al.Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials. JAMA. 2017;318(10):927–38. [PubMed: 28898378]

59. Gleason CE, Dowling NM, Wharton W, Manson JE, Miller VM, Atwood CS, 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(6):e1001833; discussion e. [PubMed: 26035291]
60. Espeland MA, Shumaker SA, Leng I, Manson JE, Brown CM, LeBlanc ES, 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(15):1429–36. [PubMed: 23797469]
61. Henderson VW, St John JA, Hodis HN, McCleary CA, Stanczyk FZ, Shoupe D, et al.Cognitive effects of estradiol after menopause: A randomized trial of the timing hypothesis. Neurology. 2016;87(7):699–708. [PubMed: 27421538]
62. Imtiaz B, Taipale H, Tanskanen A, Tiihonen M, Kivipelto M, Heikkinen AM, et al.Risk of Alzheimer's disease among users of postmenopausal hormone therapy: A nationwide case-control study. Maturitas. 2017;98:7–13. [PubMed: 28274328]
63. Savolainen-Peltonen H, Rahkola-Soisalo P, Hoti F, Vattulainen P, Gissler M, Ylikorkala O, et al.Use of postmenopausal hormone therapy and risk of Alzheimer's disease in Finland: nationwide case-control study. BMJ. 2019;364:l665. [PubMed: 30842086]
64. Mikkola TS, Savolainen-Peltonen H, Tuomikoski P, Hoti F, Vattulainen P, Gissler M, et al.Lower Death Risk for Vascular Dementia Than for Alzheimer's Disease With Postmenopausal Hormone Therapy Users. J Clin Endocrinol Metab. 2017;102(3):870–7. [PubMed: 27906568]
65. Gervais NJ, Au A, Almey A, Duchesne A, Gravelsins L, Brown 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. [PubMed: 32497876]
66. Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de Andrade M, et al.Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neurology. 2007;69(11):1074–83. [PubMed: 17761551]
67. Bove R, Secor E, Chibnik LB, Barnes LL, Schneider JA, Bennett DA, et al.Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women. Neurology. 2014;82(3):222–9. [PubMed: 24336141]
68. 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(6):887–900. [PubMed: 30334074]
69. Wisch JK, Meeker KL, Gordon BA, Flores S, Dincer A, Grant EA, et al.Sex-related Differences in Tau Positron Emission Tomography (PET) and the Effects of Hormone Therapy (HT). Alzheimer Dis Assoc Disord. 2021;35(2):164–8. [PubMed: 32520734]
70. Rahman A, Schelbaum E, Hoffman K, Diaz I, Hristov H, Andrews R, et al.Sex-driven modifiers of Alzheimer risk: A multimodality brain imaging study. Neurology. 2020;95(2):e166–e78. [PubMed: 32580974]
71. Brinton RD. The healthy cell bias of estrogen action: mitochondrial bioenergetics and neurological implications. Trends Neurosci. 2008;31(10):529–37. [PubMed: 18774188]
72. Thompson MR, Niu J, Lei X, Nowakowska M, Wehner MR, Giordano SH, et al.Association of Endocrine Therapy and Dementia in Women with Breast Cancer. Breast Cancer (Dove Med Press). 2021;13:219–24. [PubMed: 33854369]
73. Yaffe K, Krueger K, Cummings SR, Blackwell T, Henderson VW, Sarkar S, et al.Effect of raloxifene on prevention of dementia and cognitive impairment in older women: the Multiple Outcomes of Raloxifene Evaluation (MORE) randomized trial. Am J Psychiatry. 2005;162(4):683–90. [PubMed: 15800139]
74. Henderson VW, Ala T, Sainani KL, Bernstein AL, Stephenson BS, Rosen AC, et al.Raloxifene for women with Alzheimer disease: A randomized controlled pilot trial. Neurology. 2015;85(22):1937–44. [PubMed: 26537053]
75. Han M, Chang J, Choi S, Cho Y, Lee G, Park SM. Association of tibolone and dementia risk: a cohort study using Korean claims data. Gynecol Endocrinol. 2021;37(6):567–71. [PubMed: 33150798]
76. Brinton RD, Yao J, Yin F, Mack WJ, Cadenas E. Perimenopause as a neurological transition state. Nat Rev Endocrinol. 2015;11(7):393–405. [PubMed: 26007613]

77. Freedman RR. Menopausal hot flashes: mechanisms, endocrinology, treatment. J Steroid Biochem Mol Biol. 2014;142:115–20. [PubMed: 24012626]

78. Drogos LL, Rubin LH, Geller SE, Banuvar S, Shulman LP, Maki PM. Objective cognitive performance is related to subjective memory complaints in midlife women with moderate to severe vasomotor symptoms. Menopause. 2013;20(12):1236–42. [PubMed: 23676633]

79. Triantafyllou N, Armeni E, Christidi F, Rizos D, Kaparos G, Palaiologou A, et al.The intensity of menopausal symptoms is associated with episodic memory in postmenopausal women. Climacteric. 2016;19(4):393–9. [PubMed: 27338648]

80. Rubin LH, Sundermann EE, Cook JA, Martin EM, Golub ET, Weber KM, et al.Investigation of menopausal stage and symptoms on cognition in human immunodeficiency virus-infected women. Menopause. 2014;21(9):997–1006. [PubMed: 24496085]

81. Jaff NG, Rubin LH, Crowther NJ, Norris SA, Maki PM. Menopausal symptoms, menopausal stage and cognitive functioning in black urban African women. Climacteric. 2020;23(1):38–45. [PubMed: 31455107]

82. LeBlanc ES, Neiss MB, Carello PE, Samuels MH, Janowsky JS. Hot flashes and estrogen therapy do not influence cognition in early menopausal women. Menopause. 2007;14(2):191–202. [PubMed: 17194963]

83. Maki PM, Drogos LL, Rubin LH, Banuvar S, Shulman LP, Geller SE. Objective hot flashes are negatively related to verbal memory performance in midlife women. Menopause. 2008; 15(5):848–56. [PubMed: 18562950]

84. Fogel J, Rubin LH, Kilic E, Walega DR, Maki PM. Physiologic vasomotor symptoms are associated with verbal memory dysfunction in breast cancer survivors. Menopause. 2020;27(11):1209–19. [PubMed: 33110036]

85. Thurston RC, Blumenthal JA, Babyak MA, Sherwood A. Emotional antecedents of hot flashes during daily life. Psychosom Med. 2005;67(1):137–46. [PubMed: 15673636]

86. Greendale GA, Wight RG, Huang MH, Avis N, Gold EB, Joffe H, et al.Menopause-associated symptoms and cognitive performance: results from the study of women's health across the nation. Am J Epidemiol. 2010;171(11):1214–24. [PubMed: 20442205]

87. Maki PM, Thurston RC. Menopause and Brain Health: Hormonal Changes Are Only Part of the Story. Front Neurol. 2020;11:562275. [PubMed: 33071945]

88. Thurston RC. Vasomotor symptoms: natural history, physiology, and links with cardiovascular health. Climacteric. 2018;21(2):96–100. [PubMed: 29390899]

89. Zhu D, Chung HF, Dobson AJ, Pandeya N, Anderson DJ, Kuh D, et al.Vasomotor menopausal symptoms and risk of cardiovascular disease: a pooled analysis of six prospective studies. Am J Obstet Gynecol. 2020;223(6):898 e1- e16. [PubMed: 32585222]

90. Thurston RC, Aizenstein HJ, Derby CA, Sejdic E, Maki PM. Menopausal hot flashes and white matter hyperintensities. Menopause. 2016;23(1):27–32. [PubMed: 26057822]

91. Thurston RC, Wu M, Aizenstein HJ, Chang Y, Barinas Mitchell E, Derby CA, et al.Sleep characteristics and white matter hyperintensities among midlife women. Sleep. 2020;43(6).

92. Greendale. Effects of the Menopause Transition and Hormone Use on Cognitive Performance in Midlife Women. Neurology. 2009.

93. Rocca WA, Grossardt BR, Shuster LT. Oophorectomy, estrogen, and dementia: a 2014 update. Mol Cell Endocrinol. 2014;389(1–2):7–12. [PubMed: 24508665]

94. Trabuco EC, Moorman PG, Algeciras-Schimnich A, Weaver AL, Cliby WA. Association of Ovary-Sparing Hysterectomy With Ovarian Reserve. Obstet Gynecol. 2016;127(5):819–27. [PubMed: 27054925]

95. Moorman PG, Myers ER, Schildkraut JM, Iversen ES, Wang F, Warren N. Effect of hysterectomy with ovarian preservation on ovarian function. Obstet Gynecol. 2011;118(6):1271–9. [PubMed: 22067716]

96. Rocca WA, Gazzuola-Rocca L, Smith CY, Grossardt BR, Faubion SS, Shuster LT, et al.Accelerated Accumulation of Multimorbidity After Bilateral Oophorectomy: A Population-Based Cohort Study. Mayo Clin Proc. 2016;91(11):1577–89. [PubMed: 27693001]

97. Wellons M, Ouyang P, Schreiner PJ, Herrington DM, Vaidya D. Early menopause predicts future coronary heart disease and stroke: the Multi-Ethnic Study of Atherosclerosis. Menopause. 2012;19(10):1081–7. [PubMed: 22692332]

98. Kritz-Silverstein D, Barrett-Connor E. Hysterectomy, oophorectomy, and cognitive function in older women. J Am Geriatr Soc. 2002;50(1):55–61. [PubMed: 12028247]

99. Geerlings MI, Ruitenberg A, Witteman JCM, van Swieten JC, Hofman A, van Duijn CM, et al.Reproductive Period and Risk of Dementia in Postmenopausal Women. JAMA. 2001;285(11):1475–81. [PubMed: 11255424]

100. Kurita K, Henderson VW, Gatz M, St John J, Hodis HN, Karim R, et al.Association of bilateral oophorectomy with cognitive function in healthy, postmenopausal women. Fertil Steril. 2016;106(3):749–56 e2. [PubMed: 27183047]

101. Phung TK, Waltoft BL, Laursen TM, Settnes A, Kessing LV, Mortensen PB, et al.Hysterectomy, oophorectomy and risk of dementia: a nationwide historical cohort study. Dement Geriatr Cogn Disord. 2010;30(1):43–50. [PubMed: 20689282]

102. Ryan J, Scali J, Carriere I, Amieva H, Rouaud O, Berr C, et al.Impact of a premature menopause on cognitive function in later life. BJOG. 2014;121(13):1729–39. [PubMed: 24802975]

103. Zeydan B, Tosakulwong N, Schwarz CG, Senjem ML, Gunter JL, Reid RI, et al.Association of Bilateral Salpingo-Oophorectomy Before Menopause Onset With Medial Temporal Lobe Neurodegeneration. JAMA Neurol. 2019;76(1):95–100. [PubMed: 30326011]

104. Glymour MM, Manly JJ. Lifecourse social conditions and racial and ethnic patterns of cognitive aging. Neuropsychol Rev. 2008;18(3):223–54. [PubMed: 18815889]

105. Brewster KL, Rindfuss RR. Fertility and Women's Employment in Industrialized Nations. Annual Review of Sociology. 2000;26:271–96.

106. Iwamoto SJ, Defreyne J, Rothman MS, Van Schuylenbergh J, Van de Bruaene L, Motmans J, et al.Health considerations for transgender women and remaining unknowns: a narrative review. Ther Adv Endocrinol Metab. 2019;10:2042018819871166. [PubMed: 31516689]

107. Avila JF, Vonk JMJ, Verney SP, Witkiewitz K, Arce Renteria M, Schupf N, et al.Sex/gender differences in cognitive trajectories vary as a function of race/ethnicity. Alzheimers Dement. 2019;15(12):1516–23. [PubMed: 31606366]

Table 1

Lifecourse reproductive health relationships with ADRD risk*

Women's Reproductive Health Events	ADRD Risk
Menarche	
Later Age of Menarche	
Gilsanz et al. 2019[31] (Kaiser Permanente Northern California health care data)	↑
Prince et al. 2018[35] (10/66 population-based study of women in Latin America and China	↔
Pregnancy	
Hypertensive Disorders of Pregnancy	
Adank et al. 2021[15] (ORACLE Substudy of Generation R Study)	↑
Basit et al. 2018[13] (Danish population register data)	↑
Dayan et al. 2018[8] (Coronary Artery Risk Development in Young Adults Study)	↑
Parity	
Read and Grundy 2017[24] (English Longitudinal Study of Ageing)	U
Menopause	
Later Age At Menopause	
Gilsanz et al. 2019[31] (Kaiser Permanente Northern California Health care data)	↓
Longer Reproductive Span	
Matyi et al. 2019[44] (Cache County Study on Memory in Aging)	↓
Surgical Menopause	
Rocca et al. 2007[66] (Mayo Clinic Cohort Study of Oophorectomy and Aging)	↑
Bove et al. 2014[67] (Religious Orders Study and Rush Memory and Aging Project)	↑
Hormone Therapy:	
Schumaker et al. 2003[55] (Women's Health Initiative Memory Study)	↑
Espeland et al. 2013[60] (Women's Health Initiative Memory Study of Younger Women)	↔
Gleason et al. 2015[59] (Kronos Early Estrogen Prevention Study)	↔
Henderson et al. 2016[61] (Early vs Late Intervention Trial with Estradiol	↔

*Summary of key findings

Legend: ↑ increased risk; ↓ decreased risk; ↔ no association; U 0-1 child and 3+ children associated with poor cognition

Table 2:

Key Knowledge Gaps in Sex-Specific Risk Factors for ADRDs

• How parity and adverse pregnancy outcomes influence late-life cognition, and the mechanisms by which they do so
• The effect of long-term use of hormone therapy in perimenopausal women with indications for hormone therapy treatment
• The long-term effects of menopause transition-associated symptoms on cognitive health
• The impact of women's reproductive history on ADRD biomarkers and neuropathology
• The extent to which birth cohort influences the relationship between women's health and cognition
• The effects of gender affirming hormone therapy on late-life cognition
• The effects of social determinants of health on the relationship between women's health and cognition