HHS Public Access

Author manuscript

Alzheimers Dement. Author manuscript; available in PMC 2017 July 01.

Published in final edited form as:

Alzheimers Dement. 2016 July ; 12(7): 758–765. doi:10.1016/j.jalz.2015.12.010.

Endogenous sex hormones and cognitive function in older women

Alain K. Koyama[a,b], **Shelley S. Tworoger**[a,b], **A. Heather Eliassen**[a,b], **Olivia I. Okereke**[a,b], **Marc G. Weisskopf**[b,c], **Bernard Rosner**[a,d], **Kristine Yaffe**[e,f], and **Francine Grodstein**[a,b]

[a]Channing Division of Network Medicine, Department of Medicine, Brigham & Women's Hospital and Harvard Medical School, 181 Longwood Ave, Boston, MA

[b]Department of Epidemiology, Harvard T. H. Chan School of Public Health, 677 Huntington Ave, Boston MA

[c]Department of Environmental Health, Harvard T. H. Chan School of Public Health, 677 Huntington Ave, Boston MA

[d]Department of Biostatistics, Harvard T. H. Chan School of Public Health, 677 Huntington Ave, Boston MA

[e]Departments of Psychiatry, Neurology, and Epidemiology and Biostatistics, University of California San Francisco, 4150 Clement St, San Francisco, CA

[f]San Francisco VA Medical Center, 4150 Clement St, San Francisco, CA

Abstract

INTRODUCTION—We examined the association between endogenous sex hormones and both objective and subjective measures of cognitive function.

METHODS—We followed 3,044 women up to 23 years in a prospective cohort study. We measured plasma levels of estrone, estrone sulfate, estradiol, androstenedione, testosterone, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEA-S) in 1989–1990, conducted neuropsychologic testing in 1999–2008, and inquired about subjective cognition in 2012.

RESULTS—Overall, we observed little relation between plasma levels of hormones and either neuropsychologic test performance or subjective cognition. However, after adjustment for age and education, we observed a borderline significant association of higher levels of plasma estrone with higher scores for both overall cognition (p trend=0.10) and verbal memory (p trend=0.08).

Corresponding author: Alain K. Koyama, 181 Longwood Ave, Boston, MA 02115, akoyama@post.harvard.edu, Phone: 617-525-2253, Fax: 617-525-2008.

CONCLUSION—There were no clear associations of endogenous hormone levels at mid-life and cognition in later life, although a suggested finding of higher levels of plasma estrone associated with better cognitive function merits further research.

Keywords

hormones; subjective cognitive complaints; cognition; dementia; Alzheimer's disease

1. Introduction

Despite the public health burden of cognitive impairment on an aging population, the etiology of cognitive decline is still not well understood. Much biological evidence suggests sex hormones may play a role in the development of cognitive decline. For example, estrogen receptors are expressed in many key regions of the brain involved in cognitive function, including the hippocampus and other limbic structures, cingulate and the frontal cortex[1]. Laboratory studies also suggest both direct and indirect neuroprotective effects of estrogens including promotion of hippocampal synaptic plasticity and protection against apoptosis and oxidative stress[2]. Less research exists on the cognitive effects of androgens in women. As with estrogens, androgens can bind to receptors in the brain and may exert neuroprotective effects such as protection against beta-amyloid induced apoptosis and the hyperphosphorylation of tau protein[3, 4]. Additionally, androgen receptors are particularly concentrated in the hippocampus[5], a critical region for learning and memory and one of the earliest regions impacted in the pathogenesis of Alzheimer disease.

Conflicting with the biologic evidence, the pivotal Women's Health Initiative Memory Study randomized controlled trial demonstrated a detrimental effect of combination estrogen and progestin therapy on cognitive function when administered to older women[6]. Observational studies of endogenous hormones (in the absence of exogenous hormone use) may help to reconcile some of the differences in findings with the biological evidence, and could reduce some biases inherent in observational research on hormone therapy[7]. Furthermore, the limited use of androgen therapy in women prohibits large-scale research of exogenous androgens and cognition. While some existing research has indeed addressed the role of endogenous sex hormones in late-life cognitive decline, results have been inconsistent and many studies are limited by cross-sectional analyses or short follow-up times [8, 9].

Finally, there is increasing interest in the use of subjective cognitive concerns (SCC) as an indicator of cognitive function. Existing studies suggest SCC are associated with grey matter atrophy[10], white matter tract degeneration[11], amyloid burden[12], as well as cognitive function[13, 14]. Thus, SCC may provide a complementary outcome in cognitive aging research. We therefore conducted a study to prospectively investigate if plasma levels of sex hormones and their prohormones were associated with objective and subjective measures of cognitive function in a population of older women who provided blood samples at mid-life.

2.Methods

2.1 Study Population

The Nurses' Health Study (NHS) is an ongoing prospective study of registered nurses in the United States[15]. The study began in 1976, when 121,701 female nurses aged 30 to 55 years completed and returned a mailed questionnaire. Follow-up questionnaires are mailed biennially and a follow-up rate of approximately 90% has been maintained. Baseline for the present analyses occurred from 1989 to 1990, when 32,826 women provided blood samples by overnight mail and completed a short questionnaire. For the present analyses, measures of sex hormones were utilized from previous studies in NHS, including nested case-control studies of breast cancer, ovarian cancer, colon cancer, rheumatoid arthritis, inflammatory bowel disease, stroke and myocardial infarction. Among the 32,826 women with blood samples, 25,964 did not have any sex hormones measured, 1,713 did not have cognitive data (cognitive assessments were only administered to the oldest segment of the cohort), 2,043 were cases from the nested case-control studies, and 62 were missing data on age or age at menopause, resulting in an analytic cohort of 3,044 women with at least one sex hormone measured.

2.2 Biomarker Assessment

Upon receipt, blood samples were aliquotted into plasma, white blood cell, and red blood cell components, and stored in liquid nitrogen freezers at −130° C. Further details on the collection and storage procedures have been reported previously[16]. Measured hormones included bound levels of plasma estrone, estrone sulfate, estradiol, androstenedione, testosterone, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEA-S).

Estrone, estrone sulfate, estradiol, androstenedione and testosterone were measured by radioimmunoassay at the Quest Diagnostics Nichols Institute (San Juan Capistrano, CA) or by liquid chromatography-tandem mass spectrometry (ThermoFisher Scientific, Franklin, MA and Applied Biosystems-MDS Sciex, Foster City, CA) at the Mayo Medical Laboratories (Rochester, MN). DHEA was measured by radioimmunoassay (Diagnostic Systems Laboratories, Webster, TX) at Quest Diagnostics or by the quantitative sandwich enzyme immunoassay technique at Dr. Nader Rifai’s laboratory at the Department of Laboratory Medicine, Children’s Hospital Boston (Boston, MA). DHEA-S was measured by the Immulite 2000 a solid-phase, chemiluminescent immunoassay (Siemens Medical Solutions, Los Angeles, CA) at Quest Diagnostics and Mayo Medical Laboratories, or by a coated-tube radioimmunoassay at Dr. Rifai’s laboratory. In a prior study in the NHS cohort, levels of sex hormones measured using different assays were highly correlated (R=0.87 for estrone to 0.98 for testosterone)[17]. The assay detection limits were for 10 pg/ml estrone, 40 pg/ml for estrone sulfate, 2 pg/ml for estradiol, 5 ng/dL for androstenedione, 0.5–2 ng/dL for testosterone, 10 ng/dL for DHEA, and 5–15 ug/dL for DHEA-S. Values below the detection limit were set to half the limit.

Average overall coefficients of variation from the measured batches were within acceptable ranges (estrone: 11.3%, estrone-S: 12.6%, estradiol: 13.5%, androstenedione: 9.3%,

testosterone: 13.3%, DHEA: 10.9%, DHEA-S: 6.6%). We adjusted for inter-batch variation using the average-batch calibration method, described by Rosner et. al.[18]. In brief, we assumed the combined batches represented an average batch, and calibrated all hormone levels to have a comparable distribution to the average batch. This was done by regressing hormone levels on their strongest predictors (age and BMI) and indicator variables for each batch. Hormone levels were calibrated by subtracting the difference of the value of the coefficient for the batch and the average of all batch coefficients, effectively adjusting for inter-batch variability independent of differences in age and BMI distribution between batches.

2.3 Cognitive Assessment

From 1995 to 2001, a cognitive substudy was initiated in which 19,415 women aged 70 years and older without a history of stroke were administered cognitive testing via telephone. The battery included six cognitive tests. We administered the Telephone Interview of Cognitive Status (TICS)[19], a telephone version of the Mini Mental State Examination (MMSE)[20]; verbal memory was measured using the immediate and delayed recall of the TICS 10-word list, and immediate and delayed recalls of the East Boston Memory Test[21]. The category fluency test, a measure of semantic memory, required participants to recite as many names of animals as possible in one minute[22]. Backward Digit Span, a test of working memory and information processing, required participants to repeat a series of numbers in the reverse order they were given[23]. After the baseline cognitive interview, up to three follow-up assessments were conducted approximately every two years. In addition, in 2012 all women in the parent cohort were asked a series of questions regarding SCC on the mailed questionnaire, which included difficulties in memory, remembering a short list, remembering recent events, understanding or following spoken instructions, understanding a group conversation or the plot of a television program, and finding one’s way on familiar streets.

2.4 Measurement of Covariates

In primary analyses, we controlled for covariates near blood draw, which were chosen a priori from factors plausibly associated with both endogenous hormone levels and cognitive function based on existing literature. Demographic variables included age and education (registered nurse/associate’s degree, bachelor's degree, graduate degree). Because education was only collected from women in the cognitive substudy, in the analysis of SCC we used data on occupational status in 2012 (not working, working full- or part-time). Body mass index (BMI, kg/m^2) was calculated from self-reported height and weight (<22, 22–24.9, 25–29.9, ≥30). Lifestyle factors included smoking status (current, former, never), alcohol consumption (non-drinker, 1–14 g/day, ≥15 g/day), and physical activity, which was measured using a validated physical activity questionnaire (quintiles of metabolic equivalents per week). Comorbidities included a history of self-reported physician diagnosis of diabetes, hypertension, and myocardial infarction. Because depression can be highly correlated with cognitive function, we used measures of depression near cognitive assessment instead of at blood draw. For women in the cognitive substudy, the SF-36 Mental Health Index (MHI) was used to measure depressive symptoms (quintiles). Scores for the MHI range from 0 to 100, with higher scores indicating fewer depressive symptoms[24]. For

the analysis of SCC, the 15–item Geriatric Depression Scale (GDS) was used because this scale was used on the 2012 questionnaire in the parent study. Scores on the GDS range from 0 to 15, with scores above 5 suggestive of depression[25]. In both analyses, we also controlled for current antidepressant use.

2.5 Statistical Analysis

To test the association between quartiles of plasma hormone levels and the composite outcomes of overall cognition and verbal memory on the neuropsychologic test battery, we used multivariate linear regression models. To reduce measurement error, overall cognition was estimated by creating a composite score at each time point, averaging the z-scores of each of the six individual cognitive tests (using the variation at baseline to calculate z-scores). Because the NHS cohort is a relatively young and well-educated population, there was not substantial change overall in cognitive scores over the follow-up period. Moreover, the follow-up time from blood draw to cognitive assessment was longer than the follow-up time from the first to last cognitive assessment. Therefore, we conducted analyses with the primary outcome of cognitive status by averaging the composite scores from each time point to create a single measure of cognitive status in older age. Verbal memory was estimated similarly, using the average of the z-scores for the each of the four tests of verbal memory.

In addition, we used multivariate logistic regression to test the association between plasma hormone levels and reporting one or more SCC (versus none) on the 2012 parent questionnaire. For all analyses, we used two models: a basic model adjusted for age and education/occupation, and a full model further adjusted for other potential confounders (BMI, alcohol use, physical activity, age at menopause, depression, antidepressant use). Tests of trend were conducted by modeling the median value of each quartile of hormone level as a continuous variable. In all analyses examining estrone, estrone sulfate, and estradiol, women reporting postmenopausal hormone use at blood draw were excluded to minimize misclassification or confounding from factors associated with hormone therapy use.

To assess possible sources of bias, we conducted several secondary analyses. First, while we did not adjust for cardiovascular disease or diabetes in our primary analyses because they may be causal intermediates, we adjusted for these factors in a secondary analysis. In another analysis, we adjusted for covariates measured near the initial cognitive assessment rather than at blood draw, due to the extended period of time from blood draw until the cognitive interviews. Because the role of any risk factors can differ among individuals already in the early stages of cognitive disease, we conducted another analysis excluding women with a TICS score of 30 or lower[26] at baseline. Additionally, we were particularly concerned about the influence of depressive symptoms on subjective measures of cognition. Therefore, for a secondary analysis of the association between plasma hormones and SCC, we additionally excluded women who had GDS scores over 5, which is suggestive of depression. Because some women who were not current hormone therapy users at blood draw later reported hormone therapy use over the follow-up period, we conducted another analysis excluding these women to ensure that hormone levels at blood draw best reflected long-term hormone levels. Lastly, in another secondary analysis, we used a repeated

measures model with an autoregressive covariance pattern instead of averaging scores over all time points, in order to assess the trajectories of cognitive scores over time. SAS 9.3 (SAS Institute Inc., Cary, NC) was used for all statistical analyses.

3. Results

3.1 Population Characteristics

Among the 3,044 women, 1,261 had measures for estrone, 912 for estrone sulfate, 1,338 for estradiol, 855 for androstenedione, 2,569 for testosterone, 1,248 for DHEA, and 2,2265 for DHEA-S. At blood draw, women ranged in age from 43 to 69 years (mean = 60.1). The mean follow-up time was 9.5 ± 1.4 years from blood draw to the first cognitive interview and 22.6 ± 0.4 years to the SCC measured in 2012. All women were postmenopausal at blood draw and 98.9% were Caucasian. Additional characteristics of the population, by quartiles of estradiol and testosterone, are shown in Table 1a and Table 1b, respectively. On average, women with higher levels of plasma estrone had higher BMI, lower alcohol intake, and a greater likelihood of reporting a history of diabetes. Women with higher levels of plasma DHEA were on average younger, but did not otherwise substantially differ.

3.2 Hormone Levels and Composite Cognitive Scores

Table 2 displays the mean differences in overall cognition, by quartile of plasma hormone level. In the model adjusted for age and education, plasma hormone levels were not significantly associated with overall cognition. However, women with higher levels of plasma estrone had higher mean scores for overall cognition, which was borderline statistically significant (p trend=0.10). In the full model, further adjusted for BMI, alcohol use, physical activity, age at menopause, depression status and antidepressant use, results remained largely unchanged. In secondary analyses, results remained similar after further adjustment for hypertension and diabetes, after using the most recent covariates, after exclusion of women with low TICS scores, exclusion of women who reported hormone therapy use between blood draw and cognitive assessment, or using a repeated measures model (data not shown).

Plasma hormone levels were not significantly associated with verbal memory in age and education-adjusted models (Table 3), similar to results for overall cognition. Women with higher levels of plasma estrone had higher mean verbal memory scores, with borderline statistical significance (p trend=0.08). In the full model, results were similar with no significant associations between plasma hormone levels and verbal memory. Results did not appreciably change after secondary analyses.

3.3 Plasma Hormone Levels and SCC

Table 4 shows odds ratios for the association between quartile of plasma hormone level and reporting one or more SCC. In the age and occupation-adjusted model, women with higher levels of plasma estrone sulfate in earlier life had a lower odds of SCC (Q4 vs Q1: OR=0.65 [95% CI: 0.43, 1.01]; p trend=0.03). In the full model, these odds ratios were somewhat attenuated (Q4 vs Q1: OR=0.75 [95% CI: 0.47, 1.19]; p trend=0.13). In the basic model, women with higher levels of DHEA had a borderline significant increased odds of reporting

one or more SCC (Q4 vs Q1: OR=1.50 [95% CI: 1.03, 2.18]; p trend=0.05). In the full model, this association was similar (Q4 vs Q1: OR=1.55 [95% CI: 1.05, 2.28]; p trend=0.03). Similar results were seen for DHEA-S (basic model: Q4 vs Q1: OR=1.30 [95% CI: 0.98, 1.72]; p trend=0.09; full model: Q4 vs Q1: OR=1.38 [95% CI: 1.03, 1.84]; p trend=0.04). In secondary analyses, results did not appreciably change. Plasma levels of other hormones were not significantly associated with SCC.

4. Discussion

We examined whether plasma levels of sex hormones and their prohormones in mid-life were associated with objective and subjective measures of cognitive function in a population of older women. Overall, levels of endogenous hormones were not significantly associated with cognitive function. However, we found a suggestion of modest associations between higher levels of plasma estrone and both overall cognition and verbal memory, and similar findings for the association between higher levels of plasma estrone sulfate and a decreased odds of SCC. There also was a suggestive positive association for DHEA and its primary circulating metabolite, DHEA-S, with SCC.

Despite biological evidence supporting a role of estradiol in cognitive function[2], we did not observe an association between levels of plasma estradiol and either objective or subjective measures of cognitive function in postmenopausal women. Prior epidemiologic studies have reported very mixed results, suggesting a protective[27], harmful[28], null[29], or J-shaped association[30]. The measurement of total estradiol may partly explain the divergent findings, since levels of free and bioavailable estradiol may better represent their potential biologic activity. Moreover, an increasing number of studies demonstrate that estradiol can be produced in the hippocampus[31, 32]. Therefore, it is possible that locally synthesized estradiol has greater potential capacity to affect neurodegenerative processes than circulating estradiol.

To our knowledge, three prior prospective studies have investigated the association between endogenous estrone or estrone sulfate and cognitive function. One study did not report a significant association, although may have been limited by a small sample size (n=148) and short follow-up (2 years)[27]. Two studies showed higher levels of estrone were associated with worse cognitive outcomes[28, 29]. However, these studies included older populations than our study, and it is possible that the association between estrogen levels and cognitive function can differ with respect to age or time since menopause[33]. The majority of studies examining the association between endogenous estrogens and cognitive function have investigated estradiol, due to its biologic potency relative to estrone or estrone sulfate. However, estrone sulfate occurs in much higher circulating levels in postmenopausal women, and growing biological evidence suggests that neuroprotective effects of estrogens are not limited to estradiol but may also be attributed to estrone or estrone sulfate[34]. Moreover, as results for both SCC and objective measures of cognitive function were qualitatively similar in our study, further investigation on estrone is merited.

Testosterone and androstenedione were not associated with either objective or subjective measures of cognitive function. To our knowledge, no prospective studies have previously

investigated the association between androstenedione and cognition in older adults. In contrast to studies of estrogens, epidemiologic studies investigating the role of testosterone have been more consistent with generally null findings[30, 35], in line with the current study. The association between higher levels of DHEA and DHEA-S and SCC was unexpected, as the collective findings from biologic and epidemiologic studies suggest either a null or protective association[9]. It is possible that this is a chance finding, because this association was only significant when using subjective measure of cognitive function, which can be highly variable.

Strengths of this study include the prospective design, long follow-up period including hormone data from mid-life, large sample size, and multiple methods of measuring cognitive status. Because this is an observational study, we cannot discount the possible effects of residual confounding. Another limitation is use of peripheral levels of hormones in the blood which may not correlate with levels in the brain, possibly explaining null findings. Lastly, a single measurement at baseline may not represent long-term levels of plasma hormones, which may bias results towards the null if long-term levels are most important to cognitive status. However, prior studies in NHS suggest that a single measurement of plasma hormones can reliably represent average levels over up to a 10-year period[36, 37], and our secondary analyses excluding women who used hormone therapy subsequent to blood draw should also help to focus findings on long-term endogenous levels.

In conclusion, we found suggestive evidence that higher plasma levels of estrone and estrone sulfate are positively associated with both objective and subjective measure of cognitive function in older women. Plasma levels of other sex hormones were not clearly associated with cognitive function. Further large prospective studies of the wide range of endogenous hormones measured earlier in life may be particularly useful in consolidating inconsistencies in the collective findings to date and to help understand whether hormones may be important to cognition.

Acknowledgments

Funding This work was supported by the National Institute of Health (UM1 CA186107, R01 CA49449, T32 MH017119).

References

1. Hogervorst, E. Hormones, cognition and dementia : state of the art and emergent therapeutic strategies. Cambridge, UK; New York: Cambridge University Press; 2009. p. 2xii, 280 p. of plates
2. Grossman M. Hormone Therapy and the Brain: A Clinical Perspective on the Role of Estrogen. Ann Intern Med. 2000; 133(8):660. [PubMed: 11033607]
3. Rosario ER, Pike CJ. Androgen regulation of beta-amyloid protein and the risk of Alzheimer's disease. Brain Res Rev. 2008; 57(2):444–453. [PubMed: 17658612]
4. Papasozomenos S, Shanavas A. Testosterone prevents the heat shock-induced overactivation of glycogen synthase kinase-3 beta but not of cyclin-dependent kinase 5 and c-Jun NH2-terminal kinase and concomitantly abolishes hyperphosphorylation of tau: implications for Alzheimer's disease. Proc Natl Acad Sci U S A. 2002; 99(3):1140–1145. [PubMed: 11805297]
5. Beyenburg S, et al. Androgen receptor mRNA expression in the human hippocampus. Neurosci Lett. 2000; 294(1):25–28. [PubMed: 11044578]

6. Rapp SR, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA. 2003; 289(20):2663–2672. [PubMed: 12771113]
7. O'Brien J, et al. Postmenopausal hormone therapy is not associated with risk of all-cause dementia and Alzheimer's disease. Epidemiol Rev. 2014; 36(1):83–103. [PubMed: 24042430]
8. Boss L, et al. Endogenous sex hormones and cognitive function in older adults: a systematic review. West J Nurs Res. 2014; 36(3):388–426. [PubMed: 23996907]
9. Maggio M, et al. DHEA and cognitive function in the elderly. J Steroid Biochem Mol Biol. 2014
10. Peter J, et al. Gray matter atrophy pattern in elderly with subjective memory impairment. Alzheimers Dement. 2014; 10(1):99–108. [PubMed: 23867795]
11. Selnes P, et al. White matter imaging changes in subjective and mild cognitive impairment. Alzheimers Dement. 2012; 8(5 Suppl):S112–S121. [PubMed: 23021621]
12. Amariglio RE, et al. Subjective cognitive complaints and amyloid burden in cognitively normal older individuals. Neuropsychologia. 2012; 50(12):2880–2886. [PubMed: 22940426]
13. Jacinto AF, et al. Subjective memory complaints in the elderly: a sign of cognitive impairment? Clinics (Sao Paulo). 2014; 69(3):194–197. [PubMed: 24626946]
14. Amariglio RE, et al. Specific subjective memory complaints in older persons may indicate poor cognitive function. J Am Geriatr Soc. 2011; 59(9):1612–1617. [PubMed: 21919893]
15. Colditz GA, Manson JE, Hankinson SE. The Nurses' Health Study: 20-year contribution to the understanding of health among women. J Womens Health. 1997; 6(1):49–62. [PubMed: 9065374]
16. Hankinson SE, et al. Plasma sex steroid hormone levels and risk of breast cancer in postmenopausal women. J Natl Cancer Inst. 1998; 90(17):1292–1299. [PubMed: 9731736]
17. Tworoger SS, et al. Inclusion of endogenous hormone levels in risk prediction models of postmenopausal breast cancer. J Clin Oncol. 2014; 32(28):3111–3117. [PubMed: 25135988]
18. Rosner B, et al. Determination of blood pressure percentiles in normal-weight children: some methodological issues. Am J Epidemiol. 2008; 167(6):653–666. [PubMed: 18230679]
19. Brandt J, Spencer M, Folstein M. The Telephone Interview for Cognitive Status. Neuropsychiatry Neuropsychol Behav Neurol. 1988; 1:111–117.
20. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12(3):189–198. [PubMed: 1202204]
21. Albert M, et al. Use of brief cognitive tests to identify individuals in the community with clinically diagnosed Alzheimer's disease. Int J Neurosci. 1991; 57(3–4):167–178. [PubMed: 1938160]
22. Spreen, O.; Strauss, E. A Compendium of Neuropsychological Tests: Administration, Norms and Commentary. New York, NY: Oxford University Press; 1991.
23. The Psychological Corporation. WAIS-III/WMS-III technical manual: Updated. San Antonio, TX: 2002.
24. Ware, J., et al. SF-36 Health Survey: Manual & Interpretation Guide. Boston, MA: Nimrod Press; 1993.
25. Lesher EL, Berryhill JS. Validation of the Geriatric Depression Scale--Short Form among inpatients. J Clin Psychol. 1994; 50(2):256–260. [PubMed: 8014251]
26. Stampfer MJ, et al. Effects of moderate alcohol consumption on cognitive function in women. N Engl J Med. 2005; 352(3):245–253. [PubMed: 15659724]
27. Ryan J, et al. Hormone levels and cognitive function in postmenopausal midlife women. Neurobiol Aging. 2012; 33(3):617.e11–622.e11. [PubMed: 20888079]
28. Laughlin GA, Kritz-Silverstein D, Barrett-Connor E. Endogenous oestrogens predict 4-year decline in verbal fluency in postmenopausal women: the Rancho Bernardo Study. Clin Endocrinol (Oxf). 2010; 72(1):99–106. [PubMed: 19508596]
29. Yaffe K, et al. Serum estrogen levels, cognitive performance, and risk of cognitive decline in older community women. J Am Geriatr Soc. 1998; 46(7):816–821. [PubMed: 9670866]
30. Carcaillon L, et al. High plasma estradiol interacts with diabetes on risk of dementia in older postmenopausal women. Neurology. 2014; 82(6):504–511. [PubMed: 24477111]

31. Yue X, et al. Brain estrogen deficiency accelerates Abeta plaque formation in an Alzheimer's disease animal model. Proc Natl Acad Sci U S A. 2005; 102(52):19198–19203. [PubMed: 16365303]

32. Bian C, et al. Intriguing roles of hippocampus-synthesized 17β-estradiol in the modulation of hippocampal synaptic plasticity. J Mol Neurosci. 2014; 54(2):271–281. [PubMed: 24729128]

33. Maki PM. Critical window hypothesis of hormone therapy and cognition: a scientific update on clinical studies. Menopause. 2013; 20(6):695–709. [PubMed: 23715379]

34. Barha CK, Galea LA. Influence of different estrogens on neuroplasticity and cognition in the hippocampus. Biochim Biophys Acta. 2010; 1800(10):1056–1067. [PubMed: 20100545]

35. Yaffe K, et al. Endogenous sex hormone levels and risk of cognitive decline in an older biracial cohort. Neurobiol Aging. 2007; 28(2):171–178. [PubMed: 17097195]

36. Hankinson SE, et al. Reproducibility of plasma hormone levels in postmenopausal women over a 2-3-year period. Cancer Epidemiol Biomarkers Prev. 1995; 4(6):649–654. [PubMed: 8547832]

37. Zhang X, et al. Postmenopausal plasma sex hormone levels and breast cancer risk over 20 years of follow-up. Breast Cancer Res Treat. 2013; 137(3):883–892. [PubMed: 23283524]

Systematic review

We reviewed existing literature investigating the association between sex hormones and cognitive function in women. While several observational studies exist, many are cross-sectional, have short-follow-up periods, and/or involve the use of hormone therapy, which can be particularly subject to bias. Moreover, limited use of androgen therapy in women prohibits large-scale research of exogenous androgens and cognitive function.

Interpretation

Overall, we found little relation between levels of plasma hormones and either objective or subjective measures of cognitive function. However, we found modest evidence of a positive association between higher levels of plasma estrone and better performance on cognitive testing, consistent with hypotheses supportive of a neuroprotective role of estrogens.

Future directions

Further large prospective studies investigating a wide range of endogenous hormones measured in mid-life are needed to consolidate the inconsistent findings to date and to help understand if hormones play a role in cognition.

Table 1

a – Characteristics of Participants, by Quartile of Estradiol Level (n=1,338)

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Age (mean ± SD)	61.8 ± 4.7	61.9 ± 4.6	61.6 ± 5.0	61.0 ± 5.2
Age at menopause (mean ± SD)	47.9 ± 5.4	48.2 ± 5.8	48.1 ± 5.8	48.9 ± 5.1
Education (n, %)[1]				
RN	138 (73.4%)	150 (73.2%)	142 (77.6%)	130 (76.9%)
Bachelor's	36 (19.2%)	40 (19.5%)	25 (13.7%)	30 (17.8%)
Graduate	14 (7.5%)	15 (7.3%)	16 (8.7%)	9 (5.3%)
Smoking (n, %)				
Never	152 (45.5%)	161 (48.4%)	164 (48.8%)	153 (45.7%)
Former	137 (41.0%)	148 (44.4%)	135 (40.2%)	147 (43.9%)
Current	45 (13.5%)	24 (7.2%)	37 (11.0%)	35 (10.5%)
Body mass index (n, %)	23.4 ± 3.3	24.4 ± 3.1	26.3 ± 4.2	29.2 ± 5.2
Alcohol (n, %)				
Non-drinker	123 (36.8%)	123 (36.9%)	141 (42.0%)	173 (51.6%)
1–14 g/day	182 (54.5%)	179 (53.8%)	159 (47.3%)	131 (39.1%)
≥15 g/day	29 (8.7%)	31 (9.3%)	36 (10.7%)	31 (9.3%)
Physical activity, MET-hr/week (mean ± SD)	18.2 ± 21.1	19.1 ± 21.5	17.5 ± 21.8	14.1 ± 17.6
Diabetes (n, %)	5 (1.5%)	8 (2.4%)	16 (4.8%)	21 (6.3%)
Hypertension (n, %)	91 (27.3%)	97 (29.1%)	104 (31.0%)	133 (39.7%)
Myocardial infarction (n, %)	10 (3.0%)	8 (2.4%)	11 (3.3%)	9 (2.7%)
SF-36 Mental Health Index (mean ± SD)[2,3]	82.2 ± 12.5	83.9 ± 10.9	80.9 ± 11.8	82.3 ± 10.5
Current antidepressant use (n, %)[2]	10 (5.3%)	4 (2.0%)	13 (7.1%)	10 (5.9%)

b – Characteristics of Participants, by Quartile of Testosterone Level (n=2,569)

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Age (mean ± SD)	60.6 ± 5.3	60.0 ± 5.3	60.3 ± 5.5	60.4 ± 5.8
Age at menopause (mean ± SD)	46.6 ± 6.4	47.3 ± 6.2	47.8 ± 5.7	47.9 ± 5.8
Education (n, %)[1]				
RN	231 (77.5%)	196 (72.9%)	216 (75.0%)	224 (75.4%)
Bachelor's	46 (15.4%)	53 (19.7%)	51 (17.7%)	52 (17.5%)
Graduate	21 (7.1%)	20 (7.4%)	21 (7.3%)	21 (7.1%)
Smoking (n, %)				
Never	303 (47.3%)	311 (48.2%)	312 (48.8%)	295 (45.9%)
Former	288 (44.9%)	275 (42.6%)	262 (40.9%)	267 (41.5%)
Current	50 (7.8%)	59 (9.2%)	66 (10.3%)	81 (12.6%)
Body mass index (n, %)	25.3 ± 4.4	25.4 ± 4.3	25.4 ± 4.3	25.2 ± 4.6
Alcohol (n, %)				
Non-drinker	237 (37.0%)	267 (41.4%)	268 (41.9%)	264 (41.1%)
1–14 g/day	348 (54.3%)	324 (50.2%)	309 (48.3%)	311 (48.4%)

b – Characteristics of Participants, by Quartile of Testosterone Level (n=2,569)

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
≥15 g/day	56 (8.7%)	54 (8.4%)	63 (9.8%)	68 (10.6%)
Physical activity, MET-hr/week (mean ± SD)	17.1 ± 20.0	18.0 ± 30.9	18.1 ± 20.6	17.9 ± 30.5
Diabetes (n, %)	21 (3.3%)	17 (2.6%)	26 (4.1%)	21 (3.3%)
Hypertension (n, %)	206 (32.1%)	173 (26.8%)	189 (29.5%)	192 (29.9%)
Myocardial infarction (n, %)	22 (3.4%)	19 (3.0%)	19 (3.0%)	11 (1.7%)
SF-36 Mental Health Index (mean ± SD)[2,3]	81.2 ± 12.3	82.1 ± 11.8	83.8 ± 11.5	81.0 ± 11.5
Current antidepressant use (n, %)[2]	18 (6.0%)	15 (5.6%)	14 (4.9%)	15 (5.1%)

[1] only available in the cognitive substudy

[2] assessed at the most recent measurement prior to the first cognitive interview

[3] range: 0–100 (lower scores indicate more depressive symptoms)

[1] only available in the cognitive substudy

[2] assessed at the most recent measurement prior to the first cognitive interview

Table 2

Mean Differences in Overall Cognition, by Quartile of Plasma Hormone Level*

	Q1 (ref.)	Q2 vs Q1	Q3 vs Q1	Q4 vs Q1	p trend
Estrone (n=655)					
Model 1	0.00	−0.01 (−0.15, 0.13)	0.00 (−0.14, 0.14)	0.10 (−0.04, 0.24)	0.10
Model 2	0.00	−0.01 (−0.15, 0.13)	−0.04 (−0.18, 0.10)	0.09 (−0.05, 0.24)	0.18
Estrone Sulfate (n=446)					
Model 1	0.00	0.13 (−0.04, 0.30)	0.15 (−0.02, 0.32)	0.08 (−0.08, 0.25)	0.57
Model 2	0.00	0.13 (−0.04, 0.29)	0.12 (−0.05, 0.29)	0.09 (−0.09, 0.26)	0.56
Estradiol (n=688)					
Model 1	0.00	−0.05 (−0.19, 0.09)	−0.04 (−0.18, 0.10)	0.01 (−0.13, 0.15)	0.70
Model 2	0.00	−0.07 (−0.21, 0.07)	−0.03 (−0.17, 0.12)	−0.01 (−0.16, 0.14)	0.85
Androstenedione (n=400)					
Model 1	0.00	0.01 (−0.17, 0.19)	−0.03 (−0.21, 0.15)	−0.09 (−0.27, 0.09)	0.26
Model 2	0.00	−0.04 (−0.23, 0.14)	−0.07 (−0.25, 0.11)	−0.14 (−0.32, 0.05)	0.12
Testosterone (n=1,063)					
Model 1	0.00	0.00 (−0.12, 0.11)	−0.02 (−0.13, 0.10)	0.04 (−0.07, 0.16)	0.45
Model 2	0.00	−0.01 (−0.12, 0.11)	−0.04 (−0.16, 0.07)	0.02 (−0.09, 0.14)	0.68
DHEA (n=522)					
Model 1	0.00	0.02 (−0.14, 0.18)	0.04 (−0.12, 0.20)	−0.04 (−0.20, 0.13)	0.63
Model 2	0.00	0.02 (−0.14, 0.18)	0.03 (−0.13, 0.19)	−0.06 (−0.22, 0.10)	0.44
DHEA Sulfate (n=900)					
Model 1	0.00	0.13 (0.01−0.26)	0.06 (−0.07, 0.18)	0.03 (−0.10, 0.15)	0.83
Model 2	0.00	0.13 (0.01−0.25)	0.05 (−0.07, 0.18)	0.00 (−0.13, 0.13)	0.51

*values indicate standard units of averaged z-scores from each cognitive test

Model 1: adjusted for age, education
Model 2: adjusted for age, education, BMI, alcohol use, physical activity, age at menopause, depression status, antidepressant use

Table 3

Mean Differences in Verbal Memory, by Quartile of Plasma Hormone Level *

	Q1 (ref.)	Q2 vs Q1	Q3 vs Q1	Q4 vs Q1	p trend
Estrone (n=655)					
Model 1	0.00	−0.01 (−0.17, 0.15)	0.00 (−0.16, 0.16)	0.12 (−0.03, 0.28)	0.08
Model 2	0.00	0.00 (−0.16, 0.16)	−0.03 (−0.19, 0.13)	0.11 (−0.05, 0.28)	0.16
Estrone Sulfate (n=446)					
Model 1	0.00	0.19 (0.00, 0.38)	0.14 (−0.05, 0.32)	0.09 (−0.10, 0.27)	0.77
Model 2	0.00	0.19 (0.00, 0.37)	0.10 (−0.09, 0.29)	0.08 (−0.12, 0.28)	0.82
Estradiol (n=688)					
Model 1	0.00	−0.05 (−0.21, 0.10)	−0.03 (−0.19, 0.12)	0.00 (−0.16, 0.15)	0.83
Model 2	0.00	−0.07 (−0.22, 0.09)	−0.02 (−0.18, 0.14)	−0.03 (−0.20, 0.14)	0.94
Androstenedione (n=400)					
Model 1	0.00	−0.03 (−0.23, 0.17)	−0.07 (−0.26, 0.13)	−0.08 (−0.28, 0.12)	0.40
Model 2	0.00	−0.07 (−0.27, 0.14)	−0.09 (−0.29, 0.10)	−0.11 (−0.32, 0.09)	0.30
Testosterone (n=1,063)					
Model 1	0.00	0.01 (−0.11, 0.14)	0.01 (−0.12, 0.13)	0.05 (−0.08, 0.18)	0.43
Model 2	0.00	0.01 (−0.11, 0.14)	−0.01 (−0.14, 0.12)	0.04 (−0.09, 0.17)	0.59
DHEA (n=522)					
Model 1	0.00	−0.07 (−0.25, 0.11)	−0.02 (−0.19, 0.16)	−0.06 (−0.24, 0.12)	0.67
Model 2	0.00	−0.06 (−0.24, 0.12)	−0.02 (−0.20, 0.16)	−0.07 (−0.25, 0.11)	0.53
DHEA Sulfate (n=900)					
Model 1	0.00	0.14 (0.01, 0.28)	0.06 (−0.08, 0.20)	0.05 (−0.08, 0.19)	0.84
Model 2	0.00	0.14 (0.00, 0.27)	0.06 (−0.08, 0.20)	0.03 (−0.11, 0.17)	0.90

* values indicate standard units of averaged z-scores from each cognitive test measuring verbal memory

Model 1: adjusted for age, education
Model 2: adjusted for age, education, BMI, alcohol use, physical activity, age at menopause, depression status, antidepressant use

Table 4

Odds of Subjective Cognitive Concerns, by Quartile of Plasma Hormone Level*

	Q1 (ref.)	Q2 vs Q1 OR (95% CI)	Q3 vs Q1 OR (95% CI)	Q4 vs Q1 OR (95% CI)	*p* trend
Estrone (n=949)					
Model 1	1.00	0.88 (0.60–1.28)	1.03 (0.71–1.51)	0.78 (0.54–1.14)	0.27
Model 2	1.00	0.86 (0.58–1.27)	1.09 (0.74–1.63)	0.81 (0.54–1.21)	0.42
Estrone Sulfate (n=701)					
Model 1	1.00	1.04 (0.67–1.62)	0.99 (0.64–1.54)	0.65 (0.42–1.01)	0.03
Model 2	1.00	1.11 (0.71–1.76)	1.05 (0.67–1.67)	0.75 (0.47–1.19)	0.13
Estradiol (n=1,008)					
Model 1	1.00	0.91 (0.63–1.31)	1.03 (0.71–1.49)	0.84 (0.58–1.21)	0.39
Model 2	1.00	0.91 (0.62–1.33)	0.98 (0.66–1.45)	0.85 (0.55–1.30)	0.49
Androstenedione (n=655)					
Model 1	1.00	0.63 (0.40–0.99)	0.71 (0.45–1.12)	0.86 (0.54–1.37)	0.82
Model 2	1.00	0.70 (0.43–1.13)	0.72 (0.45-1.16)	0.95 (0.59-1.55)	0.95
Testosterone (n=2,053)					
Model 1	1.00	1.07 (0.83–1.39)	0.92 (0.72–1.19)	1.07 (0.83–1.39)	0.75
Model 2	1.00	1.06 (0.81–1.38)	0.91 (0.70–1.18)	1.06 (0.82–1.39)	0.80
DHEA (n=966)					
Model 1	1.00	1.32 (0.91–1.91)	1.52 (1.05–2.20)	1.50 (1.03–2.18)	0.05
Model 2	1.00	1.32 (0.90–1.93)	1.57 (1.07–2.30)	1.55 (1.05–2.28)	0.03
DHEA Sulfate (n=1,795)					
Model 1	1.00	1.12 (0.85–1.47)	1.04 (0.79–1.36)	1.30 (0.98–1.72)	0.09
Model 2	1.00	1.12 (0.85–1.48)	1.03 (0.77–1.36)	1.38 (1.03–1.84)	0.04

Model 1: adjusted for age, occupation

Model 2: adjusted for age, occupation, BMI, alcohol use, physical activity, age at menopause, depression status, antidepressant use

* Odds of any versus no SCC across 6 questionnaire items regarding self-perceived cognitive status