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Featured Article

Endogenous sex hormones and cognitive function in older women

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Abstract

Introduction: We examined the association between endogenous sex hormones and both objective and subjective measures of cognitive function.
Methods: We followed 3044 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 = .10) and verbal memory (P trend = .08).
Discussion: There were no clear associations of endogenous hormone levels at midlife 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's 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

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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. Although 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 (SCCs) as an indicator of cognitive function. Existing studies suggest SCCs are associated with gray 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 midlife.

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 30–55 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 used 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, 1713 did not have cognitive data (cognitive assessments were only administered to the oldest segment of the cohort), 2043 were cases from the nested case-control studies, and 62 were missing data on age or age at menopause, resulting in an analytical cohort of 3044 women with at least one sex hormone measured.

2.2. Biomarker assessment

On receipt, blood samples were aliquoted 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, USA) or by liquid chromatography–tandem mass spectrometry (ThermoFisher Scientific, Franklin, MA, USA and Applied Biosystems-MDS SCIEX, Foster City, CA, USA) at the Mayo Medical Laboratories (Rochester, MN, USA). DHEA was measured by radioimmunoassay (Diagnostic Systems Laboratories, Webster, TX, USA) 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, USA). 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 μg/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 interbatch 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 body mass index [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 interbatch 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 [20]; verbal memory was measured using the immediate and delayed recalls of the TICS 10-word list and immediate and delayed recalls of the East Boston