Objective: To investigate an association between endogenous estradiol (E2) levels and cognition and behavior in elderly individuals.

Patients: We studied 135 community-based men and women aged 52 to 85 years in urban Bangkok, Thailand; 72 had dementia and 63 did not.

Materials and Methods: Dementia was diagnosed using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria after appropriate investigations. Blood samples for assay were collected in the morning after 6 hours of fasting. Levels of E2 were measured by radioimmunoassay (double antibody technique). The Thai version of the Mini-Mental State Examination was used to assess cognition; the Neuropsychiatric Inventory was used to assess neuropsychiatric symptoms; and the Functional Assessment Questionnaire was used to assess instrumental activities of daily living.

Results: There was no correlation between age and level of E2 in either men or women. Individuals with lower estradiol levels had more behavioral disturbances (men: \( r = -0.467, n=45; P = 0.001 \); women: \( r = -0.384, n=90; P < 0.001 \)) and worse cognition (men: \( r = 0.316, n=45; P = 0.03 \); women: \( r = 0.243, n=90; P = 0.02 \)) and function (men: \( r = -0.417, n=45; P = 0.004 \); women: \( r = -0.437, n=90; P < 0.001 \)). The threshold level of endogenous E2 in elderly individuals for the risk of developing dementia was less than 15 pg/mL (<55 pmol/L) in men and less than 1 pg/mL (<4 pmol/L) in women.

Conclusion: Lower E2 levels are correlated with poor cognitive, behavioral, and functional status in older individuals.

Endogenous Estradiol in Elderly Individuals

Cognitive and Noncognitive Associations

V. Senanarong, MD; S. Vannasaeng, MD; N. Poungvarin, MD; S. Ploybutr, MSC; S. Udompunthurak, MSC; P. Jamjumras, RN; L. Fairbanks, PhD; J. L. Cummings, MD

Estradiol replacement therapy (ERT) has been reported to be associated with a decreased risk for dementia and better cognitive function in postmenopausal women. In the Baltimore Longitudinal Study of Aging,1 a sample of 472 postmenopausal or perimenopausal women was followed for 16 years. After adjustment for educational level, investigators found a relative risk of Alzheimer disease (AD) in estrogen users of 0.46 compared with nonusers. Pagani-Hill and Henderson2 found that the risk for AD decreased with longer duration of estrogen use. Results of observational studies demonstrate that postmenopausal women perform better on name recall3 and immediate and delayed paragraph recall4 but not on clock drawing5 after ERT. Results of randomized controlled trials indicate that estrogen therapy improved cognitive function in nondemented postmenopausal women6-9 but that it is not helpful in women with AD.10-12

A recent meta-analysis by Yaffe et al9 concluded that results of observational and clinical trials of ERT and cognitive function in AD were inconclusive. Three randomized controlled trials10-12 of ERT published in 2000 all used conjugated equine estrogen, either 0.625 or 1.25 mg. The sample sizes ranged from 42 to 120 patients with AD and controls, with treatment duration ranging from 12 weeks to 12 months. None of these studies found improvement in cognitive measurements or clinical global assessment findings after estrogen therapy. Vaginal spotting and deep vein thrombosis were observed as adverse effects in some treated patients. The results of these studies suggest that ERT benefits women without dementia but not women with AD.

Although there have been several studies assessing cognitive responses to ERT, few studies have examined the relationship between endogenous estrogen status and behavioral or cognitive symptoms in either cognitively intact women or patients with dementia. We conducted a study...
PARTICIPANTS, MATERIALS, AND METHODS

The review board of the National Research Council of Thailand and an ethical committee at the Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand, approved this study. This study was part of a multidisciplinary project studying health promotion in the elderly conducted by the Faculty of Medicine, Siriraj Hospital (1997-2000). A door-to-door survey of the community-dwelling elderly population within 10 km of Siriraj Hospital was conducted in 1997. Their names were recorded and they were included in our ongoing study in the Integrated Health Research Program for the Elderly at the Faculty of Medicine, Siriraj Hospital. A total of 3518 elderly individuals from 3 amphurs (city regions) agreed to participate in the study of mental and nervous systems. The mean ± SD age of this group was 68.8 ± 7.2 years, and the full range of the Thai Mental State Examination (TMSE) was represented in participants from this initial survey.

Of the 135 men and women aged 52 to 85 years solicited from this community-based cohort, 72 had dementia and 63 did not. Internists or neurologists obtained the medical histories and conducted physical examinations. Dementia was diagnosed using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria. Exclusion criteria were delirium and a history of psychiatric disorders before the onset of memory problems. Blood tests and computed tomography were performed for individuals with suspected dementia. Alzheimer disease was diagnosed according to the criteria of the joint task force of the National Institute of the Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association.

Data were obtained via structured questionnaires administered by professional nurses. The TMSE, a translated and culturally modified version of the Mini-Mental State Examination for the Thai population, was used to assess cognitive function. The Neuropsychiatric Inventory (NPI) was applied to caregivers, relatives, or proxies of the elderly individuals to assess neuropsychiatric symptoms. The Functional Assessment Questionnaire was used to assess activities of daily living. These measures were translated from English into Thai and then back into English, and any discrepancies were resolved.

After 6 hours of fasting, 10-mL blood samples were collected from participants via venipuncture between 7 and 11 AM. Samples were immediately centrifuged, and the serum was stored at −20°C. Analysis of samples was conducted within 3 months of blood being drawn. Levels of E2 were measured by radioimmunoassay (double antibody technique) using a commercial kit (Double Antibody Estradiol; Diagnostic Products Corp, Los Angeles, Calif). Statistical analysis was performed using a software program (SPSS 9.0; SPSS Inc, Chicago, Ill). The χ² test and analysis of variance were used to test for heterogeneity. Spearman correlation coefficients were used to assess correlations among measures.

Table 1. Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Without Dementia (N = 63)</th>
<th>With Dementia (N = 72)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>25 (40)</td>
<td>20 (28)</td>
</tr>
<tr>
<td>F</td>
<td>38 (60)</td>
<td>52 (72)</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>65.8 ± 5.2</td>
<td>70.6 ± 8.6</td>
</tr>
<tr>
<td>Education, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4 y</td>
<td>45 (71)</td>
<td>44 (61)</td>
</tr>
<tr>
<td>&gt;4 y</td>
<td>18 (29)</td>
<td>28 (39)</td>
</tr>
</tbody>
</table>

The 63 cognitively healthy individuals and the 72 with dementia were similar in sex distribution and educational level (Table 1). Alzheimer disease was diagnosed in 37 participants with dementia, who were significantly older than those without dementia (P<.001), and age was used as a covariate in subsequent analyses. Most patients with non-AD dementias had vascular dementia. Other elderly individuals with dementia had Parkinson disease with dementia, dementia with Lewy bodies, normal-pressure hydrocephalus, and neurosyphilis. Mean E2 levels in men and women were markedly different in demented and nondemented elderly individuals, with men having higher levels than postmenopausal women in all diagnostic groups (Table 2).

Five of the 135 participants had been receiving ERT: 2 did not have dementia, and 3 did. Four participants had undergone ERT for less than 6 months and had stopped more than 5 years before blood samples were drawn for E2 analysis. One individual with dementia had taken estrogens for 2 years and had stopped a few months before this investigation because of vaginal bleeding.

To investigate the relationships of estrogen status to cognition and behavior in each sex, we analyzed the association between E2 levels and TMSE and NPI scores in men and women. There was no correlation between age and levels of E2 in either men or women. There was a negative correlation between total NPI scores and E2 levels in both groups (men: r = −0.467, n = 45; P = .001; women: r = −0.384, n = 90; P < .001). Patients with lower E2 levels had higher NPI scores and more marked neuropsychiatric symptoms. In this sample, relationships between E2 levels and NPI subscale scores did not reach statistical significance.

There was a positive correlation between global cognitive function as measured by the TMSE and E2 levels in both groups (men: r = 0.316, n = 45; P = .03; women: r = 0.243, n = 90; P = .02). Lower E2 levels were associated with worse cognition. There were negative correlations between Functional Assessment Questionnaire scores and levels of E2 in men and women (men: r = −0.417,
the endogenous E2 level of the nondemented group was 68.86 ± 7.94 pg/mL (24.59 ± 2.85 pmol/L), and that of the group with dementia was 13.69 ± 4.02 pg/mL (1.0 ± 0.07 pmol/L), indicating that individuals with lower serum E2 levels had greater functional deficits.

The study groups had similar educational levels but differed significantly in mean age (P < 0.001). We generated partial correlation coefficients controlling for age and found that the significant relationships remained between endogenous E2 levels and TMSE scores (r = 0.187, n = 131; P = 0.03), endogenous E2 levels and NPI measurement (r = 0.194, n = 131; P = 0.03), and endogenous E2 levels and Functional Assessment Questionnaire scores (r = 0.269, n = 131; P = 0.002).

We analyzed the associations among all 135 samples and found statistically significant correlations between E2 levels and TMSE scores (r = 0.304, n = 135; P < 0.001) and between E2 levels and NPI scores (r = 0.333, n = 135; P < 0.001). Associations between E2 levels and TMSE scores were not statistically significant after controlling for NPI scores (P = 0.18); similarly, associations between E2 levels and NPI scores were not statistically significant after controlling for TMSE scores (P = 0.15). This indicates that low E2 levels are jointly associated with poor cognitive function and more severe neuropsychiatric symptoms.

When the relationships of E2 levels to cognitive and behavioral measures were investigated in the control group and the dementia group individually, we found no association between endogenous E2 levels and NPI scores or between endogenous E2 and TMSE scores. The mean ± SD endogenous E2 level of the nondemented group was 12 ± 13 pg/mL (44 ± 48 pmol/L), and that of the group with dementia was 4 ± 7 pg/mL (15 ± 26 pmol/L). Most participants had serum E2 levels less than 15 pg/mL (<55 pmol/L); this markedly skewed deviation likely explains the lack of discoverable associations among
cognition, neuropsychiatric symptoms, and E2 levels. However, E2 seemed to reduce the risk for developing neuropsychiatric symptoms: in these data, individuals with high NPI scores were more likely to have low E2 levels.

We hypothesized that there was a threshold risk of endogenous E2 levels in elderly persons for developing dementia. Estradiol levels less than 15 pg/mL (<55 pmol/L) in men and less than 1 pg/mL (<4 pmol/L) in women carried a relative risk for dementia of 10.83 and 6.23, respectively (Table 3).

We demonstrated that elderly individuals with lower E2 levels have more impaired cognition, more severe neuropsychiatric symptoms, and more compromised activities of daily living. Previous epidemiologic studies1-2,19-21 found a lower estimated relative risk for developing AD of 30% to 60% in postmenopausal estrogen users. However, recent randomized trials of women with AD and estrogen treatment10-12 showed no significant difference in outcomes of cognitive and global assessments between treatment and placebo groups. These apparently conflicting results suggest that optimal levels of E2 are needed to maintain brain function but that ERT may not have therapeutic value once AD is present. Few studies have assessed the relationship between the level of endogenous E2 and cognition. Our study demonstrates a relationship between cognitive status, as measured by the TMSE, and endogenous E2 levels, suggesting that even in individuals with normal cognition, lower E2 levels are associated with worse cognition.

The data also suggest a risk threshold of endogenous E2 levels for occurrence of dementia. Levels of endogenous E2 associated with a high risk for dementia were different in women and men, perhaps because older men have higher levels of testosterone to be converted to E2. Our results vary somewhat from those of a study by Manly et al.22 who found that the risk for AD was increased 4-fold.

### Table 2. Assessments of Study Groups

<table>
<thead>
<tr>
<th>Sex, No.</th>
<th>AD Group</th>
<th>Non-AD Dementia Group</th>
<th>Nondemented Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>8</td>
<td>13</td>
<td>37</td>
</tr>
<tr>
<td>F</td>
<td>29</td>
<td>23</td>
<td>50</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>68.24 ± 7.94</td>
<td>72.23 ± 7.35</td>
<td>65.81 ± 4.33</td>
</tr>
<tr>
<td>Women</td>
<td>68.86 ± 7.94</td>
<td>72.96 ± 10.33</td>
<td>65.56 ± 5.38</td>
</tr>
<tr>
<td>FAQ score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>18.00 ± 7.29</td>
<td>18.23 ± 10.06</td>
<td>0.65 ± 1.23</td>
</tr>
<tr>
<td>Women</td>
<td>16.59 ± 9.31</td>
<td>17.30 ± 9.44</td>
<td>1.78 ± 4.79</td>
</tr>
<tr>
<td>TMSE score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>19.63 ± 10.10</td>
<td>19.38 ± 9.05</td>
<td>26.42 ± 2.17</td>
</tr>
<tr>
<td>Women</td>
<td>19.34 ± 8.72</td>
<td>15.58 ± 8.49</td>
<td>25.98 ± 2.55</td>
</tr>
<tr>
<td>NPI score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>14.00 ± 15.07</td>
<td>18.08 ± 15.25</td>
<td>0.19 ± 0.07</td>
</tr>
<tr>
<td>Women</td>
<td>15.24 ± 13.61</td>
<td>13.00 ± 11.28</td>
<td>0.78 ± 2.85</td>
</tr>
<tr>
<td>Estradiol, pg/mL †</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men (n = 45)</td>
<td>15.63 ± 8.57</td>
<td>8.64 ± 6.29</td>
<td>22.09 ± 12.95</td>
</tr>
<tr>
<td>Women (n = 90)</td>
<td>16.59 ± 9.31</td>
<td>1.97 ± 5.25</td>
<td>4.75 ± 7.30</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD except where indicated otherwise. AD indicates Alzheimer disease; FAQ, Functional Assessment Questionnaire; TMSE, Thai Mental State Examination; and NPI, Neuropsychiatric Inventory. †To convert estradiol from picograms per milliliter to picomoles per liter, multiply picograms per milliliter by 3.67.

### Table 3. Threshold Risks of Serum Estradiol Level for Developing Dementia

<table>
<thead>
<tr>
<th>Estradiol, pg/mL *</th>
<th>Nondemented Group</th>
<th>Demented Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20</td>
<td>1.0</td>
<td>...</td>
</tr>
<tr>
<td>15.1-20</td>
<td>6.5 (0.51-109.53)</td>
<td>...</td>
</tr>
<tr>
<td>≤15</td>
<td>10.83 (1.66-90.07)</td>
<td>...</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>22.09 ± 12.95</td>
<td>11.09 ± 7.74</td>
</tr>
</tbody>
</table>

*To convert estradiol from picograms per milliliter to picomoles per liter, multiply picograms per milliliter by 3.67. Ellipses indicate not applicable. The relative risk of all the men (n = 45) included demented and nondemented men; the relative risk of all the women (n = 90) included demented and nondemented women.
for E2 levels less than 20 pg/mL (<73 pmol/L). Yaffe et al.23 found an association between higher serum endogenous estrone and lower scores on digit symbol and Trail-Making B tests in 532 women 65 years or older, and they hypothesized an antagonist effect of estrone to E2.

We found a negative correlation between neuropsychiatric symptoms, as shown by NPI scores, and E2 levels. A relationship between estrogen deficiency and increased risk of developing depressive symptoms is supported by many observational studies. Sherwin24 found that mood correlated with circulating levels of E2 in surgically menopausal women. Carlson et al.25 also found a negative relationship between mood scores, as measured by the Geriatric Depression Scale, and endogenous E2 levels in elderly men and women. Palinkas and Barrett-Connor26 conducted a cross-sectional study of 1190 women in California. Mean scores on the Beck Depression Inventory increased with age in non–estrogen users, whereas no statistically significant increase in mean scores was found in estrogen users. The NPI used in the present study measures a variety of neuropsychiatric symptoms, including delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor activity. In this sample size, we did not have sufficient power to identify correlations between NPI subscale scores and E2 levels.

The association between activities of daily living and E2 levels found in this study may be attributed to the effect of cognitive status on function. Galasko et al.27 found in their 3-year follow-up study that patients with AD who deteriorated faster in functional activities had more rapid decline in cognitive performance. Other studies28 also demonstrated that dementia severity, measured by the Mini-Mental State Examination, was a good predictor of everyday functioning.

Estrogen has many plausible benefits for the brain. There are 2 estrogen receptors, α and β, which are distributed in different tissues.29 The estrogen receptor alpha is predominantly distributed in the breast and endometrium, and the estrogen receptor beta is distributed in the brain, blood vessels, and bone. This may explain the diverse responses of women to estrogen deprivation and the wide range of adverse effects of ERT. Certain brain regions, including the amygdala, hippocampus, cingulate gyrus, locus coeruleus, and basal forebrain, have high levels of estrogen and progestin receptors.30 Estrogen increases the number of dendritic spines and synapses in the hypothalamus and cortical neurons.31 Estrogen stimulates basal forebrain cholinergic neurons through effects on neurotrophins, nerve growth factor, and brain-derived neurotrophic factor.32,33 Estrogen promotes vasodilatation by inhibiting endothelin and by stimulating endothelial-derived relaxing factor.34,35 Estrogen promotes production of amyloid precursor protein36 and may reduce deposition of β-amyloid.37 Estradiol has biological effects on regulation of mood and behavior through serotonin, norepinephrine, and dopamine.38

The advantage of this study was the availability of groups of elderly persons with and without dementia of similar educational level and sex distribution. Few of the women included received ERT. There were only 5 women who had ever used estrogen. Four of these women had used estrogen briefly and stopped more than 5 years before the study. The other user was a woman with dementia who discontinued ERT a few months before the study. The study was cross-sectional, and some analyses were limited by sample size restrictions. The study depended on volunteers from a randomized community-based sample, and volunteer status may have affected the ratio of demented to non-demented individuals in the study. Volunteer status is unlikely to have been affected by E2 levels or related analyses. Individuals with purely endogenous E2 provide insight into the relationship between cognitive and noncognitive phenomena and estrogen. The results add to the emerging data set supporting the hypothesis that estrogen has beneficial effects on cognition, behavior, and function in elderly women.

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Corresponding author and reprints: Jeffrey L. Cummings, MD, Reed Neurological Research Center, Department of Neurology, UCLA School of Medicine, 710 Westwood Plaza, Los Angeles, CA 90095-1769 (e-mail: cummings@ucla.edu).

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