The endocrine facets of Alzheimer’s disease and dementia-related disorders

Konstantinos Toulis, MD MSc(Res) MSc(HCM) PhD
Endocrinologist
Sex hormones
Calcium metabolism
GH/IGF-I
Thyroid axis
Metabolic hormones

+ dementia
Sex hormones
Calcium metabolism
GH/IGF-I
Thyroid axis
(Metabolic hormones: INS, leptin)

+ dementia
Age-related neurodegenerative disease

The hallmarks of Alzheimer’s disease

- extracellular deposition of β-amyloid protein (Aβ peptide from amyloid precursor) in the form of neuritic plaques.
- hyperphosphorylation of the cytoskeletal protein tau leading to the formation of neurofibrillary tangles

Any endocrine process that contributes to the above is considered in this review.
Sex hormones + dementia
Introduction

Human brain is sexually dimorphic

Normal aging depletion of sex steroids
Background

- Estradiol reduces the formation of Aβ
  Proceedings of the National Academy of Sciences of the United States of America, 102 (2005), pp. 19198–19203

- prevents the tau hyperphosphorylation

- facilitates potentiation in the hippocampus
Background

- Among women with Alzheimer's disease, current use of hormone therapy is associated with better cognitive skills.

  Neurology, 48 (1997), pp. 1511–1517

- Women using hormone therapy at baseline achieved better cognitive endpoints than non-users or the placebo group when assigned a cholinesterase inhibitor.

  Neurology, 46 (1996), pp. 1580–1584
Estrogens and treatment

Evidence from randomized controlled trials?
Estrogens and treatment of Alzheimer’s disease

- Few RCTs, low sample sizes and statistical power and short follow-ups
- Marked heterogeneity in estrogen preparations as well as the definition of outcomes.


Neurology, 48 (1997), pp. 1511–1517
<table>
<thead>
<tr>
<th>Authors, country, year</th>
<th>Country</th>
<th>Number</th>
<th>Duration weeks</th>
<th>Type of menopause</th>
<th>age, years</th>
<th>Active intervention</th>
<th>Endpoints&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Cognition</th>
<th>Function</th>
<th>Glot&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthana et al., 1999 [45]</td>
<td>US</td>
<td>12</td>
<td>8</td>
<td>Natural</td>
<td>79</td>
<td>TD E2</td>
<td>+/0&lt;sup&gt;d&lt;/sup&gt;</td>
<td>NE</td>
<td>NE</td>
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</tr>
<tr>
<td>Henderson et al., 2000 [50]</td>
<td>US</td>
<td>40</td>
<td>16</td>
<td>Both</td>
<td>78</td>
<td>CEE</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mulnard et al., 2000 [48]</td>
<td>US</td>
<td>120</td>
<td>52</td>
<td>Surgical</td>
<td>75</td>
<td>CEE</td>
<td>0</td>
<td>0</td>
<td>0/−&lt;sup&gt;d&lt;/sup&gt;</td>
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</tr>
<tr>
<td>Wang et al., 2000 [51]</td>
<td>Taiwan</td>
<td>50</td>
<td>12</td>
<td>Natural</td>
<td>72</td>
<td>CEE</td>
<td>0</td>
<td>NE</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Asthana et al., 2001 [46]</td>
<td>US</td>
<td>20</td>
<td>8</td>
<td>Both</td>
<td>80</td>
<td>TD E2</td>
<td>+/0&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Rigaud et al., 2003 [49]&lt;sup&gt;e&lt;/sup&gt;</td>
<td>France</td>
<td>117</td>
<td>26</td>
<td>Both</td>
<td>76</td>
<td>TD E2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Zhang et al., 2006 [52]&lt;sup&gt;f&lt;/sup&gt;</td>
<td>China</td>
<td>41</td>
<td>16</td>
<td>NE</td>
<td>55</td>
<td>CEE</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Valen-Senstad et al., 2010 [53]</td>
<td>Norway</td>
<td>55</td>
<td>52</td>
<td>NE</td>
<td>81</td>
<td>E2</td>
<td>0</td>
<td>0/−&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Wharton et al., 2011 [47]</td>
<td>US</td>
<td>34</td>
<td>12</td>
<td>Both</td>
<td>77</td>
<td>TD E2</td>
<td>+/0&lt;sup&gt;d&lt;/sup&gt;</td>
<td>NE</td>
<td>NE</td>
<td></td>
</tr>
</tbody>
</table>
Estrogens and treatment of Alzheimer’s disease

Direct RCT evidence

Endpoints in most trials indicated no overall benefit or harm

Best available evidence (two largest trials) revealed no cognitive, functional, or global effect.

Neurology, 60 (2003), pp. 148–149
Estrogens and Alzheimer’s disease

Does age at menopause affect dementia risk?
Age at menopause and dementia risk

- Inconclusive results regarding age at menopause and dementia risk.
  

  Alzheimer Disease and Associated Disorders, 20 (2006), pp. 141–146

- The same applies to surgical menopause as a risk factor for early-onset Alzheimer’s disease

  Dementia and Geriatric Cognitive Disorders, 30 (2010), pp. 43–50

Estrogens and Alzheimer’s disease

Is HRT useful in preventing Alzheimer’s disease?
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

Conclusions Estrogen plus progestin therapy increased the risk for probable dementia in postmenopausal women aged 65 years or older. In addition, estrogen plus progestin therapy did not prevent mild cognitive impairment in these women. These findings, coupled with previously reported WHI
Estrogens and prevention of Alzheimer’s disease

The short time frame over which the increased risk for all-cause dementia emerged suggested that the increased risk of dementia did not reflect the primary initiation of neuropathology, but rather hastened existing neuropathology.

However

Also, 85% of women who initiate HT did so within one year of the final menstrual period in contrast to WHIMS population.
Effect of Raloxifene on Prevention of Dementia and Cognitive Impairment in Older Women: The Multiple Outcomes of Raloxifene Evaluation (MORE) Randomized Trial

Diagnosed by a blinded adjudication committee. **RESULTS:** Of the 5,386 women, 5,153 (95.7%) were classified as cognitively normal, 181 (3.4%) had mild cognitive impairment, and 52 (1.0%) had dementia, 38 with Alzheimer’s disease. Compared to those taking placebo, women receiving 120 mg/day of raloxifene had a 33% lower risk of mild cognitive impairment (relative risk, 0.67; 95% confidence interval [CI], 0.46–0.98) and somewhat lower risks of Alzheimer’s disease (relative risk=0.52, 95% CI=0.22–1.21) and any cognitive impairment (relative risk=0.73, 95% CI=0.53–1.01). Risks of mild cognitive impairment, Alzheimer’s disease, and any impairment were not significantly different in the group taking 60 mg/day of raloxifene. **CONCLUSIONS:** Raloxifene at a dose of 120 mg/day, but not 60 mg/day, resulted in reduced risk of cognitive impairment in postmenopausal women.
### Estrogens and prevention of Alzheimer’s disease

#### Indirect observational evidence in humans

<table>
<thead>
<tr>
<th>Study, authors, year</th>
<th>Number of Alzheimer’s disease cases</th>
<th>Number of non-demented controls</th>
<th>Source of information</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group Health, Brenner et al., 1994 [78]a</td>
<td>107</td>
<td>120</td>
<td>Pharmacy recordsa</td>
<td>1.1</td>
<td>0.6–1.8</td>
</tr>
<tr>
<td>Leisure World, Paganini-Hill &amp; Henderson, 1996 [64]b</td>
<td>248</td>
<td>1193</td>
<td>Self-report</td>
<td>0.65</td>
<td>0.5–0.9</td>
</tr>
<tr>
<td>North Manhattan, New York, 1996 [80]a</td>
<td>274</td>
<td>1540</td>
<td>Self-report</td>
<td>0.68</td>
<td>0.5–1.1</td>
</tr>
<tr>
<td>Baltimore Longitudinal Study of Aging, 2001 [61]b</td>
<td>286</td>
<td>1206</td>
<td>Self-report</td>
<td>0.7</td>
<td>0.5–0.9</td>
</tr>
</tbody>
</table>
| Rochester, Minnesota, 2001 [82]c | 169 | 1200 | Self-report | 0.8 | 0.6–1.
| United Kingdom [81]a | 53 | 7697 | Self-report | 0.4 | 0.2–0.55 |
| Women’s Health Initiative Memory Study, Henderson, Espeland et al., 2007 [82]d | 33 | 7647 | Self-report | 0.8 | 0.6–1.1 |
| Cache County, Shao et al., 2012 [83]b,e | 176 | 1768 | Self-report | 0.8 | 0.6–1.1 |

The trend suggested a **mild protective effect**; however, the validity is undermined by
- recall bias and
- healthy user bias
Estrogens and prevention of Alzheimer’s disease

incongruent evidence

Why does the evidence differ between RCT and observational studies?

The Critical Window Hypothesis of Hormone Therapy and Cognition: A Scientific Update on Clinical Studies

**Timing of initiation** may be an important modifier of HT effect on cognitive function
The basis for the “critical window hypothesis”

Hormone Replacement Therapy and Incidence of Alzheimer Disease in Older Women
The Cache County Study

Prospective cohort design

P: ~1400 men and 1800 women

I: Ca/VitD/HRT

C: Incidence of dementia

O: adjusted Hazard Ratio
Critical window hypothesis

“Because many women use HT for relatively brief durations around the menopause, the protective effect of ever-use therapy suggests the possibility of a critical period during the climacteric years, which are characterized by relatively rapid estrogen depletion.”
In stratified analyses, a significant protective association was seen only in the youngest age tertile (50-63 years; OR= 0.35, 95% CI= 0.19 to 0.66)

Women who used any type of HT within 5 years of menopause had 30% less risk of AD (95% CI 0.49-0.99).
Which cognitive domain is more sensitive?

The cognitive domain most sensitive to the effects of HT (positive or negative) is verbal memory (paragraph recall word list), established predictor of dementia.

Still considered to be inconclusive, association is not causation.
The cognitive domain most sensitive to the effects of HT (positive or negative) is verbal memory (paragraph recall word list), an established predictor of dementia.

**NOTE:** East Boston Memory Test, easily reached maximum if repeated.

<table>
<thead>
<tr>
<th>Author (Year) Cohort</th>
<th>N</th>
<th>Mean Age (Span)</th>
<th>HT Use</th>
<th>Design</th>
<th>Tests</th>
<th>Results</th>
</tr>
</thead>
</table>
| MacLennan (2006) REMEMBER | 428 | 70.7 (60+)      | Early: 72% E alone: 39% | 1 FTF Assessment | • global function  
• verbal memory  
• verbal fluency  
• naming  
• psychomotor speed  
• executive function | • Early > Late: global function  
• Early > Never: psychomotor speed  
• Also some subgroup effects |
| Ryan (2009) Three Cities | 3130 | 74 (65+)        | Past: 16% Current: 15% Nonusers: 69% | 3 FTF assessments, 2 y apart | • global function  
• verbal memory  
• visual memory  
• verbal fluency  
• psychomotor speed  
• executive function | • Current > Never: verbal fluency, visual memory, psychomotor  
• Late > Never: verbal fluency  
• Trans. E+P > Never: verbal fluency, visual memory, psychomotor |
| Khoo (2010) LAW | 410 | 79 (61-)        | Early: 39% Late: 32% Nonusers: 52% | 3 FTF assessments, 2 y apart | • global function  
• verbal memory  
• visual memory  
• verbal fluency  
• psychomotor speed  
• executive function | • Current > Never: Global Function  
• Late > Never: Memory  
• Current > Never: baseline verbal memory and speed, advantage waned with time  
• Late < Premenopausal: change in verbal memory |
| Greendale (2009) SWAN | 2,502 | 46 (42-52)      | Curr Nonusers: 27% 27% Early: before FMP | 3 FTF assessments, 2 y apart | • global function  
• verbal memory  
• working memory | • Any HT < Never  
• No effect of timing |
| Kang & Grodstein NHS (2012) | 16,514 | 74 (70-81)    | Past: 35% E alone: 25% E+P: 9% Nonusers: 31% | ≤3 phone assessments, 2 y apart | • global function  
• verbal memory |
Functional neuroimaging studies

Neuroimaging outcomes are typically more sensitive than neuropsychological tests


**Perimenopausal use of hormone therapy is associated with enhanced memory and hippocampal function later in life.**

Data demonstrated that early and continued use of HT since the perimenopause was associated later in life with enhanced verbal recognition and enhanced function of the hippocampus.
Recap

**estrogen + Alzheimer’s disease and dementia-related disorders**

- Estrogen preparations have limited place in the treatment of AD
- Estrogen preparations may prevent dementia when used in early menopause
- Novel selective estrogen receptor modulators may hold promise and need further investigation
Calcium homeostasis

+ dementia
Low 25(OH)VitD levels and Alzheimer’s disease

Low Serum Vitamin D Concentrations in Alzheimer’s Disease: A Systematic Review and Meta-Analysis

Low 25OH Vitamin D2 Levels Found in Untreated Alzheimer’s Patients, Compared to Acetylcholinesterase-Inhibitor Treated and Controls
Low 25(OH)VitD levels and Alzheimer’s disease

Low Serum Vitamin D Concentrations in Alzheimer’s Disease: A Systematic Review and Meta-Analysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Year</th>
<th>Weight</th>
<th>Effect Size IV, Fixed, 95% CI</th>
<th>Effect Size IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martyn et al. [18]</td>
<td>1989</td>
<td>9.4%</td>
<td>0.63 [0.12, 1.14]</td>
<td>0.63 [0.12, 1.14]</td>
</tr>
<tr>
<td>Ferrier et al. [19]</td>
<td>1990</td>
<td>5.8%</td>
<td>0.38 [-0.27, 1.03]</td>
<td>0.38 [-0.27, 1.03]</td>
</tr>
<tr>
<td>Kipen et al. [20]</td>
<td>1995</td>
<td>8.1%</td>
<td>0.79 [0.24, 1.34]</td>
<td>0.79 [0.24, 1.34]</td>
</tr>
<tr>
<td>Sato et al. [22]</td>
<td>2005</td>
<td>14.4%</td>
<td>3.10 [2.69, 3.51]</td>
<td>3.10 [2.69, 3.51]</td>
</tr>
<tr>
<td>Evatt et al. [24]</td>
<td>2008</td>
<td>32.3%</td>
<td>0.15 [-0.12, 0.42]</td>
<td>0.15 [-0.12, 0.42]</td>
</tr>
<tr>
<td>Buell et al. [26]</td>
<td>2010</td>
<td>21.9%</td>
<td>0.39 [0.06, 0.72]</td>
<td>0.39 [0.06, 0.72]</td>
</tr>
</tbody>
</table>

Total (95% CI): 100.0% 1.08 [0.92, 1.23]

Heterogeneity: Chi² = 298.92, df = 6 (P < 0.00001); I² = 98%

Test for overall effect: Z = 13.53 (P < 0.00001)
Vitamin D levels are significantly lower in patients suffering from Alzheimer’s disease arising from extremely low levels of 25OHD2 along with low levels of 25OHD3. Treatment with acetylcholinesterase inhibitors reverses this deficit.
Low 25(OH)VitD levels and Alzheimer’s disease

- Increased vascular stiffness
- Potential gender-specific effect
- Hypertension
Vitamin D epimers and Alzheimer’s disease

- Common measurements do not differentiate between D2 and D3
- Epimers of VitD (stereoisomers) cannot be measured unless LC/MS is applied and their role is unknown
Vitamin D epimers and Alzheimer’s disease

Exploring the Role of Vitamin D in Type 1 Diabetes, Rheumatoid Arthritis, and Alzheimer Disease: New Insights From Accurate Analysis of 10 Forms

Cross-sectional design

P: 12 patients with Alzheimer’s disease

I: Epimers of 25(OH)D

C: Discrimination between diseases
Elevated PTH and vascular dementia

Plasma Parathyroid Hormone Is Associated with Vascular Dementia and Cerebral Hyperintensities in Two Community-Based Cohorts

Prospective

Prospective

160 patients with dementia (91 Alzheimer’s)

Conclusions:

In two community-based samples, PTH predicted clinically diagnosed vascular dementia as well as neuroimaging indices of cerebral small vessel disease. Our data suggest a role for PTH in the development of vascular dementia.
Plasma Parathyroid Hormone Is Associated with Vascular Dementia and Cerebral Hyperintensities in Two Community-Based Cohorts
Elevated PTH levels: pathogenesis

Elevated PTH level and vascular dementia

- Increased vascular stiffness
- Hypertension
- Predisposing factors to small-vessel cerebral disease
Plasma Parathyroid Hormone Is Associated with Vascular Dementia and Cerebral Hyperintensities in Two Community-Based Cohorts

Table 3. PIVUS: Relation of Plasma PTH to White Matter Hyperintensities

<table>
<thead>
<tr>
<th>Model</th>
<th>A Unadjusted</th>
<th>B Vascular Disease Risk Factors</th>
<th>C Mineral Metabolism</th>
<th>D Vascular Disease Risk Factors + Mineral Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous models</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 sd increase</td>
<td>0.22 (0.006–0.44)\textsuperscript{a}</td>
<td>0.23 (0.011–0.45)\textsuperscript{a}</td>
<td>0.30 (0.07–0.54)\textsuperscript{a}</td>
<td>0.31 (0.07–0.54)\textsuperscript{a}</td>
</tr>
<tr>
<td>Multi-category models</td>
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<td></td>
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</tr>
<tr>
<td>T1, &lt;3.54 pmol/L</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>T2, 3.54–5.96 pmol/L</td>
<td>0.20 (–0.30–0.70)</td>
<td>0.21 (–0.30–0.72)</td>
<td>0.21 (–0.30–0.72)</td>
<td>0.19 (–0.33–0.70)</td>
</tr>
<tr>
<td>T3, &gt;5.96 pmol/L</td>
<td>0.57 (0.07–1.1)\textsuperscript{a}</td>
<td>0.58 (0.07–1.09)\textsuperscript{a}</td>
<td>0.72 (0.19–1.25)\textsuperscript{b}</td>
<td>0.71 (0.17–1.25)\textsuperscript{a}</td>
</tr>
<tr>
<td>Threshold models</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 vs T1–2, &gt;5.96 pmol/L</td>
<td>0.47 (0.045–0.89)\textsuperscript{a}</td>
<td>0.47 (0.04–0.90)\textsuperscript{a}</td>
<td>0.61 (0.15–1.07)\textsuperscript{b}</td>
<td>0.60 (0.16–1.05)\textsuperscript{b}</td>
</tr>
</tbody>
</table>
Elevated PTH level and vascular dementia

Plasma Parathyroid Hormone Is Associated with Vascular Dementia and Cerebral Hyperintensities in Two Community-Based Cohorts

First prospective confirmation to date

Direct effects on cerebral processing speed

Improved cognitive function after parathyroidectomy

(Walker et al, 2009)

(Braverman et al, 2009)
**Recap**

disorders of calcium metabolism + Alzheimer’s disease and dementia-related disorders

- Low levels of VitD (especially D2) may be associated with AD
- Elevation of PTH may be associated with vascular dementia
GH/IGF axis + dementia
IGF and Alzheimer’s disease

The quality control of **protein homeostasis** deteriorates with aging, causing the accumulation of misfolded proteins and neurodegeneration.

This is associated with the progressive destruction of synaptic circuits controlling memory and higher mental function.
IGF1-R

- Tyrosine kinase receptor
- Phosphoinositide 3 - PKB
- Target protein: mTOR↑, GSK3β↑, FOXO ↓

In the nervous system, survival, migration, neuronal polarity, stress resistance, protein translation, synaptic plasticity, learning and memory, autophagy, cell cycle, protein trafficking, metabolism and myelination.
IGF1-R: molecular basis

**mTOR**: mammalian target of rapamycin

When down-regulated ↓, the activation of autophagy pathways that clear misfolded proteins is permitted.

**FOXO**: forkhead box O

When upregulated ↑, the transcription of anti-stress genes that have a positive effect on protein homeostasis is permitted.

In KO models, deleting a IGF1R copy creates mice that live an average of 26% longer. *Nature 2003*
IGF1-R

Blocking the sustained hyperactivation of the PKB/mTOR arm of the IGF-R pathway, might be an approach to protect against the progression of protein misfolding in AD, Aβ-induced synaptotoxicity and the spread of tau pathology

IGF1-R: pilot clinical studies

Blocking the sustained hyperactivation of IGF-IR through:

1. Intranasal insulin therapy can directly target the CNS (central nervous system), but not peripheral IR.
   
   Arch. Neurol. 2012, 69, 29-38

2. Injectable IGF-I
   
   Exp. Gerontol. 46, 96-99

IGF1-R

Increasing IGF-I levels will result in downregulation of brain IGF-I signaling.

(Cohen et al., 2009)

The relationship between systemic and brain IGF-I function is complex, suggesting that both compartments are regulated independently.

(Adams et al., 2009)
Recap

IGF1R+ Alzheimer’s disease and dementia-related disorders

- No conclusive evidence, still under active investigation
Thyroid axis

+ dementia
Thyroid axis and dementia

Definitions:

- Clinical Hyperthyroidism: TSH ↓ + TFTs ↑
- Subclinical hyperthyroidism: TSH ↓ + TFT normal
- Clinical hypothyroidism: TSH ↑ + TFTs ↓
- Subclinical hypothyroidism: TSH ↑ + TFTs normal
- Euthyroidism (+/- thyroid autoimmunity): TSH + TFTs normal
Thyroid axis and dementia

Clinical hypothyroidism and hyperthyroidism have long been recognized as potentially reversible causes of cognitive impairment.

PubMed Link to Article

Cummings JBenson DFLoVerme S Reversible dementia: illustrative cases, definition, and review. *JAMA* 1980;243 (23) 2434- 2439
Clinical Hyperthyroidism: TSH ↓ + TFTs ↑

- Subclinical hyperthyroidism: TSH ↓ + TFT normal

- Clinical hypothyroidism: TSH ↑ + TFTs ↓

- Subclinical hypothyroidism: TSH ↑ + TFTs normal

- Euthyroidism (+/- thyroid autoimmunity): TSH + TFTs normal
Rationale for the association between SCH and AD

- T3 has been shown to affect splicing of certain β-amyloid precursor protein isoforms, preferentially expressed in the AD brain.

  Endocrinology 139:2692–2698

- Hyperthyroid state results in diminishing antioxidative enzymes

  Endocrine 2011 40:285–289

  - This is a potential pathway of β amyloid-mediated neurotoxicity
SCH and dementia

The Thyroid in Mind: Cognitive Function and Low Thyrotropin in Older People

Systematic review of all studies investigating the association between SCH and dementia
<table>
<thead>
<tr>
<th>Author and year of publication</th>
<th>Study size (n) and setting</th>
<th>Mean age (range)</th>
<th>Follow-up interval (yr)</th>
<th>Participants' thyroid status</th>
<th>Thyroid function indicators (normal range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Categorical analysis of subclinical thyroid disease vs. euthyroidism; or quantiles of serum T4 concentration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kalmijn, 2000 (51)</td>
<td>1893 community</td>
<td>68.8 (54–94)</td>
<td>2–4</td>
<td>SH and euthyroid</td>
<td>TSH, FT4, TT4 TSH (0.4–4.0 mU/liter) FT4 (11–25 pmol/liter)</td>
</tr>
<tr>
<td>Tan, 2008 (52)</td>
<td>1864 community</td>
<td>71</td>
<td>12.7</td>
<td>SH and euthyroid</td>
<td>TSH (0.5–5.0 mU/liter)</td>
</tr>
<tr>
<td>Vadiveloo, 2011 (53)</td>
<td>12,115 community; SH- 2004; euthyroid, 10,111</td>
<td>66.5 ± 15.9</td>
<td>Median, 5.6 yr</td>
<td>SH and euthyroid</td>
<td>TSH (0.4–4.0 mU/liter); FT4 (10–25 pmol/liter); FT3 (0.9–2.6 nmol/liter) (at least 2 measurements of TSH, minimally 4 months apart)</td>
</tr>
<tr>
<td>de Jong, 2009 (54)</td>
<td>615 community</td>
<td>77.3–78.6</td>
<td>5</td>
<td>SH and euthyroid</td>
<td>TSH, FT4, FT4. TSH (0.4–4.3 mU/liter); FT4 (0.85–1.94 ng/d)</td>
</tr>
<tr>
<td>de Jong, 2006 (55)</td>
<td>1,025 community</td>
<td>72.3 (60–90)</td>
<td>5.5</td>
<td>Euthyroid only</td>
<td>TSH, FT4, FT3. TSH (0.4–4.3 mU/liter); FT4 (0.85–1.94 ng/d)</td>
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<tr>
<td>Volpato, 2002 (56)</td>
<td>464 community</td>
<td>77.5</td>
<td>3</td>
<td>Euthyroid only</td>
<td>TSH, FT4. TSH (0.3–5.0 mU/liter); FT4 (4.5–12.5 ng/d)</td>
</tr>
<tr>
<td>Multivariate analysis with thyroid function markers or cognitive performance as continuous variables</td>
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<tr>
<td>Hogervorst, 2008 (57)</td>
<td>1,047 community</td>
<td>(64–94)</td>
<td>2</td>
<td>Euthyroid only</td>
<td>TSH, FT4. TSH (0.3–4.8 mU/liter); FT4 (13–23 pmol/liter)</td>
</tr>
<tr>
<td>Gussekloo, 2004 (58)</td>
<td>558 community</td>
<td>85</td>
<td>3.7</td>
<td>All thyroid status</td>
<td>TSH, FT4, FT3. TSH (0.3–4.8 mU/liter); FT4 (13–23 pmol/liter)</td>
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<tr>
<td>Wahlin, 2005 (59)</td>
<td>200 community</td>
<td>75–96</td>
<td>3, then 6 yr</td>
<td>Euthyroid only</td>
<td>TSH, FT4. TSH (0.4–5 mU/liter); FT4 (12–25 pmol/liter)</td>
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<tr>
<td>Annerbo, 2006 (60)</td>
<td>93 hospital-based</td>
<td>Men, 64.7; women, 65.4</td>
<td>5</td>
<td>All thyroid status</td>
<td>TSH (no normal range provided)</td>
</tr>
</tbody>
</table>
Twenty-three studies that met our criteria have examined the association between SH and cognition. Fourteen of these studies, including several well-designed and well-powered cross-sectional and longitudinal analyses, have shown a consistent finding of an association of SH or low serum TSH within the reference interval, with cognitive impairment or dementia. In particular, this association was seen in more than three fourths of the prospective longitudinal studies, providing reliable evidence from robust studies. Several of the studies that did not
Subclinical Hypothyroidism and dementia

Neuropsychological Function and Symptoms in Subjects with Subclinical Hypothyroidism and the Effect of Thyroxine Treatment

Cross-sectional study design

P  7342 subjects (89 with SH)
I  Cognitive functions test /Beck Depression inventory
C  TSH 3.5-10 mU/L
### Subclinical Hypothyroidism and dementia

<table>
<thead>
<tr>
<th></th>
<th>SHT group with serum TSH 3.5–10 mIU/liter</th>
<th>SHT group with serum TSH 5.0–10 mIU/liter</th>
<th>Control group</th>
<th>T4 g/l baseline</th>
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<tbody>
<tr>
<td><strong>Result</strong></td>
<td>n</td>
<td>Score</td>
<td>n</td>
<td>Score</td>
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<td>Attention and working memory</td>
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<tr>
<td>Digit Span forward</td>
<td>↑ 78</td>
<td>5.6 ± 30</td>
<td>5.9 ± 107</td>
<td>5.6 ± 36</td>
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<td></td>
<td></td>
<td>1.0</td>
<td>1.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Digit Span backward</td>
<td>↑ 78</td>
<td>4.1 ± 30</td>
<td>4.2 ± 107</td>
<td>4.3 ± 36</td>
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<td></td>
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<td>1.0</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Seashore Rhythm test</td>
<td>↓ 75</td>
<td>388 ± 28</td>
<td>384 ± 102</td>
<td>395 ± 34</td>
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<td></td>
<td></td>
<td>±</td>
<td>±</td>
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<tr>
<td>Psychomotor/cognitive speed</td>
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<tr>
<td>Trail Making test A</td>
<td>↓ 78</td>
<td>48.7 ± 30</td>
<td>51.5 ± 105</td>
<td>44.0 ± 36</td>
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<td></td>
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<td>±</td>
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<tr>
<td></td>
<td></td>
<td>20.0</td>
<td>21.2</td>
<td>15.7</td>
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<tr>
<td>Stroop test, parts 1</td>
<td>↓ 76</td>
<td>50.8 ± 28</td>
<td>51.2 ± 103</td>
<td>48.0 ± 35</td>
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<tr>
<td></td>
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<td>±</td>
<td>±</td>
<td>±</td>
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<tr>
<td></td>
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<td>18.8</td>
<td>11.5</td>
<td>9.1</td>
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<tr>
<td>Digit Symbol test</td>
<td>↑ 77</td>
<td>42.8 ± 29</td>
<td>43.4 ± 104</td>
<td>43.7 ± 36</td>
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<td>±</td>
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<td></td>
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<td>12.5</td>
<td>12.6</td>
<td>12.3</td>
</tr>
</tbody>
</table>
LT4 treatment and cognition

Neuropsychological Function and Symptoms in Subjects with Subclinical Hypothyroidism and the Effect of Thyroxine Treatment

“T4 substitution had no effect on any of the parameters measured”

Cognitive function in Hashimoto’s thyroiditis under levothyroxine treatment

study failed to detect any noticeable changes in the cognitive and emotional function of two women with HT under LT4 treatment. The course of cognitive function of the two HT patients,
Neuropsychological Function and Symptoms in Subjects with Subclinical Hypothyroidism and the Effect of Thyroxine Treatment

**Conclusion:** In subjects with SHT where the serum TSH level is in the 3.5–10.0 mIU/liter range, there is **no neuropsychological dysfunction**, and compared with healthy controls, there is no difference in symptoms related to hypothyroidism.
SH/SCH and dementia

1864 cognitively intact, clinically euthyroid Framingham original cohort participants (mean age, 71 years)

Mean follow-up of 12.7 years
Women with TSH values in the lowest (<1.0 mIU/L) and highest (>2.1 mIU/L) tertiles had a greater than 2-fold higher risk of AD. In contrast, we observed no such relationship between TSH and AD risk in men. When analyses were limited to TSH levels 0.5 to 5.0 mIU/L, no statistical significance was noted.
Thyroid disorders + Alzheimer’s disease and dementia-related disorders

- Overt hypo and hyperthyroidism are reversible causes of dementia
- Subclinical hyperthyroidism may be associated with dementia
- There is no strong evidence to suggest that subclinical hypothyroidism and/or treatment with LT4 are associated with increased or decreased risk for AD