PRIMARY CARE MANUAL ON WELLNESS IN ELDERS
# Primary Care Manual on Wellness in Elders

## Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page No’s.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VASCULAR:</strong></td>
<td>4-20</td>
</tr>
<tr>
<td>• Promote Cerebrovascular Fitness</td>
<td></td>
</tr>
<tr>
<td>• Physician fact sheet about the potential risk of cardiovascular disease in the development of dementia in later life</td>
<td></td>
</tr>
<tr>
<td>• The primary care guide of cerebrovascular prevention strategies for dementia</td>
<td></td>
</tr>
<tr>
<td>• A patient’s guide to protecting memory</td>
<td></td>
</tr>
<tr>
<td><strong>ALCOHOL:</strong></td>
<td>21-30</td>
</tr>
<tr>
<td>• Promote moderate alcohol consumption</td>
<td></td>
</tr>
<tr>
<td>• Physician fact sheet on responsible drinking</td>
<td></td>
</tr>
<tr>
<td>• Physician guide to talking to older persons about drinking</td>
<td></td>
</tr>
<tr>
<td>• Consumer’s guide to safe drinking</td>
<td></td>
</tr>
<tr>
<td><strong>DEPRESSION:</strong></td>
<td>31-41</td>
</tr>
<tr>
<td>• Identify and treat depression</td>
<td></td>
</tr>
<tr>
<td>• Physician fact sheet on depression as a risk factor for dementia</td>
<td></td>
</tr>
<tr>
<td>• What you can do for depression</td>
<td></td>
</tr>
<tr>
<td>• A primary care guide to understanding interaction between depression and dementia</td>
<td></td>
</tr>
<tr>
<td>• Consumer guide to understanding untreated depression</td>
<td></td>
</tr>
<tr>
<td><strong>NUTRITION:</strong></td>
<td>42-58</td>
</tr>
<tr>
<td>• Advise a healthy diet and prudent nutritional supplementation</td>
<td></td>
</tr>
<tr>
<td>• Physician fact sheet on nutritional interventions for cognitive health</td>
<td></td>
</tr>
<tr>
<td>• A physician’s guide to the role of nutrition and successful cognitive aging</td>
<td></td>
</tr>
<tr>
<td>• A clinician’s guide to the role of vitamin supplementation in the prevention of dementia</td>
<td></td>
</tr>
<tr>
<td>• A consumer’s guide to dietary issues for the prevention of dementia</td>
<td></td>
</tr>
<tr>
<td>• A consumer’s guide to understanding the role of middle life obesity on the intellectual function in later life</td>
<td></td>
</tr>
<tr>
<td><strong>EXERCISE:</strong></td>
<td>59-69</td>
</tr>
<tr>
<td>• Encourage exercise and psychosocial stimulation</td>
<td></td>
</tr>
<tr>
<td>• Primary care fact sheet on the impact of lifetime education</td>
<td></td>
</tr>
<tr>
<td>• A clinician’s guide to the impact of lifetime education on intellectual function</td>
<td></td>
</tr>
<tr>
<td>• The consumer’s guide to memory exercises</td>
<td></td>
</tr>
<tr>
<td>• The consumer’s guide to understanding the role of exercise in preventing dementia</td>
<td></td>
</tr>
<tr>
<td><strong>SPIRITUALITY:</strong></td>
<td>70-77</td>
</tr>
<tr>
<td>• Understanding the role of spiritual vitality in aging</td>
<td></td>
</tr>
<tr>
<td>• Physician fact sheet on addressing spirituality in middle age or older persons as a component to successful cognitive aging</td>
<td></td>
</tr>
<tr>
<td>• A primary care guide to addressing spirituality in midlife or older persons</td>
<td></td>
</tr>
<tr>
<td>• The consumer’s guide for spirituality</td>
<td></td>
</tr>
<tr>
<td><strong>HORMONE REPLACEMENT THERAPY:</strong></td>
<td>78-87</td>
</tr>
<tr>
<td>• The value of hormonal replacement</td>
<td></td>
</tr>
<tr>
<td>• Physician fact sheet on hormone replacement therapy (HRT) as a protective intervention for dementia</td>
<td></td>
</tr>
</tbody>
</table>
- Basic facts for the primary care physician on hormone replacement therapy as a preventive strategy for dementia in women and men
- The consumer’s guide to the role of hormone replacement therapy in growing older with a healthy mind

**ANTI-INFLAMMATORY MEDICATIONS:**
- Anti-inflammatory medications as dementia retardants
- Physician fact sheet on the prescription of anti-Inflammatories in prevention of cognitive loss or dementia
- Physician guide to understanding the role of inflammation in the loss of cognitive function or the development of dementia in older persons
- The consumer guide to the role of anti-inflammatory medications in the prevention of dementia

**METABOLIC SYNDROME:**
- Managing the metabolic syndrome
- Primary care fact sheet on the role of metabolic syndrome in cognitive decline in older persons
- Understanding the role of the metabolic syndrome in cognitive decline of older persons
- The consumer’s guide for quitting the metabolic club or how I beat the metabolic syndrome
- Consumer’s guide to understanding the metabolic syndrome or how to quit club metabolique

**MEDICATION MANAGEMENT:**
- Managing Medication Management
- Physician Fact Sheet For Statin Therapy As A Protection Against Cognitive Loss In Elders
- Primary care guide to role of patient compliance and prescriptive safety
- Consumer guide for medications that control cholesterol and triglycerides

**STATINS:**
- Physician fact sheet for statin therapy as a protection against cognitive loss in elders
- The primary care guide to the use of statins as a preventive intervention for dementia
- The consumer’s guide to understanding the role of elevated cholesterol or triglycerides in dementia
- The consumer’s guide to understanding the role of elevated cholesterol or triglycerides in dementia (no. 2)

**DIABETES:**
- Physician fact sheet on the relationship between diabetes and dementia
- The primary care guide to understanding the role of diabetes and cognitive loss or dementia
- Consumer fact sheet on the role of diabetes as a risk factor for dementia
- Consumer guide to understanding the role of diabetes in dementia

**GENETICS:**
- Physician fact sheet on the role of dementia and genetics
- Explaining the role of genetics and risk factors for dementia
- The consumer’s guide to understanding genetics in dementia
- Do my genes determine my fate as I grow older

**THE TEN COMMANDMENTS OF DEMENTIA PREVENTION**
1. VASCULAR
PROMOTE CEREBROVASCULAR FITNESS

Hypertension is a significant risk factor for dementia. Multiple longitudinal studies of older subjects with untreated or under-treated hypertension demonstrate a relationship with chronic elevation of both systolic or diastolic blood pressure and risk for cognitive decline, e.g., Rotterdam Study, Framingham Study, and Honolulu Study. The possible mechanisms include hypertensive small vessel disease in white matter, accelerated atherosclerosis, hypoperfusion caused by cardiac disease, and others. The primary care physician should encourage a cerebrovascular fitness program for middle-aged and older individuals that includes meticulous, long-term control of both systolic and diastolic pressures and management of dyslipidemia through the appropriation of statins. Although retrospective studies demonstrate significant reduction in the risk of dementia among persons who take long-term statin medications, prophylactic therapy is not indicated in persons with a normal lipid profile. The precise protective mechanism of statin therapy is unknown but the effect seems unrelated to lipid levels or many risk factors for Alzheimer’s disease. Individuals with low cardiac ejection fractions and those with untreated or under-treated atrial fibrillation are at greater risk for developing both Alzheimer’s disease and vascular dementia. Meticulous cardiac care may reduce the likelihood of cognitive decline. Exercise in older persons, e.g., walking four hours per week, will significantly reduce the risk for cardiovascular complications and newer studies suggest that frequent exercise reduces the likelihood of cognitive decline. Aspirin is not shown to be effective against cognitive loss. Patient non-compliance is the major clinical obstacle to any cerebrovascular fitness program proposed by the primary care physician (Click here – 2514.1).

Recommendation

Available data indicates that meticulous control of blood pressure, lipids, and cardiovascular fitness may decrease the risk for developing dementia in later life. Education about the potential “neuroprotective” effect of blood pressure control may enhance compliance (CLICK HERE FOR MORE INFORMATION – 2513.11, 2513.91). (Click here for references – 2513.13).
The Primary Care Guide of Cerebrovascular Prevention Strategies for Dementia

1. Introduction
The primary care clinician can use clinical and pathological research to recommend cardiovascular and cerebrovascular fitness as part of their cognitive wellness message. The American Heart Association predicts that 25% of the adult population is hypertensive and about one-third are undiagnosed. The clinician can develop recommendations about the role of hypertension in dementia for patients in three broad age groups: midlife (40 to 65 yrs), older (65 to 75 yrs) and very old age groups (over 75). This segment reviews the available biomedical data that defines the role of hypertension in middle-aged and older patients as a risk factor for dementia in late life (1), (2). A lay person’s fact sheet (Consumer Guide) is attached to this document for use as patient education. (Click here for Fact Sheet – 2513.15).

The human brain is sensitive to diminished perfusion or oxygenation. Ischemic brain injury can result with as little as three minutes of diminished blood flow. Managing cerebrovascular risk factors in mid or later life may provide significant benefit to cognitive function for all individuals, especially those over age 65. The presence of metabolic syndrome in midlife may increase the risk for dementia in later life (Click Here For More Information – 2513.9). Chronic hypertension (3), risk factors for atherosclerosis (4), and cardiovascular disease (5), (6) are manageable risk factors in middle age that may predict cognitive decline in later life (7), (8), (9).

2. The Role of Hypertension in Cognitive Decline
A. Overview. Numerous longitudinal and cross-sectional studies have examined the rate or risk of cognitive decline in persons with untreated or under-treated hypertension. Longitudinal studies, such as those conducted in Sweden (9), England (10), Honolulu (11), (12), (13), Baltimore (14), and others report that older individuals who have a long-term history of untreated or under-treated hypertension have increased risk for dementia later in life, especially with other risk factors such as the presence of one or two APOE4 alleles (11)..

Individuals with untreated hypertension may have diminished cognitive function, even in the absence of dementia (13).

Hypertension can damage both large and small caliber cerebral blood vessels in the brain. Sustained hypertension is a risk factor for accelerated atherosclerosis which is common in the large caliber cerebro-vasculature. Hypertension may damage medium and small size penetrating arterioles in hemispheric white matter producing arteriolar sclerosis in brain parenchyma. Damage to the massive plexus of penetrating arterioles that perfuse brain parenchyma is particularly apparent in white matter where the ubiquitous hyperintensities seen on MRI may be produced by hypertensive small vessel damage (15), (16), (17). Hypertension may be a risk factor for mild cognitive impairment (MCI), Alzheimer’s disease, and vascular dementia in older persons (17), (18). (Click here for more information about MCI).

B. Longitudinal Studies on the Role of Hypertension in Dementia. A representative sample of studies on the relationship between blood pressure during midlife and cognitive
function in later life is demonstrated in Table 1. At least nine studies have employed cross-sectional or longitudinal methodologies to examine this issue with durations from 6 years through 30 years. The majority of studies demonstrate that sustained hypertension is associated with diminished cognitive function or increased risk for developing dementia. Each study group contained a variable mixture of individuals with a range of risk factors for atherosclerosis. The general consensus of long-term longitudinal studies supports the role of chronic hypertension in midlife as a risk factor for dementia in later life. Seven studies are cited that examine the rate of cognitive decline for older individuals based on a pre-existing history of hypertension (See Table 2). The study durations ranged from 3 years to 20 years. Location of these studies included the United States and Europe. Study groups were large, ranging from 600 to 4,000 older individuals. In general, studies of older individuals demonstrated more variation of cognitive outcomes for blood pressure levels than studies in midlife.

### Table 1. The Relationship Between Blood Pressure During Midlife and Cognitive Function in Later Life

<table>
<thead>
<tr>
<th>Location</th>
<th>Duration</th>
<th>Study Size</th>
<th>Relationship to HBP</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH</td>
<td>30 yrs.</td>
<td>392</td>
<td>Cognitive function</td>
<td>3</td>
</tr>
<tr>
<td>Sweden</td>
<td>21</td>
<td>1449</td>
<td>Risk for dementia</td>
<td>9</td>
</tr>
<tr>
<td>New Mexico</td>
<td>30</td>
<td>717</td>
<td>Cognitive function</td>
<td>68</td>
</tr>
<tr>
<td>Honolulu</td>
<td>26</td>
<td>3605</td>
<td>Cognitive function</td>
<td>11</td>
</tr>
<tr>
<td>England</td>
<td>14</td>
<td>5838</td>
<td>Small but significant Cognitive function</td>
<td>10</td>
</tr>
<tr>
<td>Finland</td>
<td>21</td>
<td>1449</td>
<td>Risk for MCI but related to other vascular risk factors</td>
<td>69</td>
</tr>
<tr>
<td>Japan</td>
<td>25 to 30</td>
<td>1660</td>
<td>Associated with Vascular dementia</td>
<td>70</td>
</tr>
<tr>
<td>USA</td>
<td>30+ yrs.</td>
<td>8845</td>
<td>Hypertension and multiple other cardiovascular risk factors Risk for dementia</td>
<td>5</td>
</tr>
<tr>
<td>Multi-site/USA</td>
<td>6 yrs.</td>
<td>10,963</td>
<td>Risk and rate of dementia</td>
<td>71</td>
</tr>
</tbody>
</table>

Among studies that include older subjects, a single study (See Table 2, Line 1) demonstrated no significant association while the remainder of the studies demonstrated diminished cognition of varying severity. Several studies (See Table 3) in elderly subjects cited loss of cognitive function with extremes of blood pressure and negative effect from low pressure as well as high pressure (19). In general, the relationship between hypertension in the older individual, i.e., over age 65, seems less clear, especially for individuals with mild hypertension. Five longitudinal studies examine the relationship between cognitive function and blood pressure in very old individuals, i.e., over age 75 (See Table 3). The duration of studies ranged from 3 to 6 years and the population sizes ranged from 377 to 4,937. The role of hypertension in the very old seemed more obscure than in studies in older individuals (20). Lower blood pressure appeared problematic, as well as significant hypertension (21) and some studies suggest that hypertensive individuals with dementia demonstrate normalization of blood pressure over time (5). Sympathetic autonomic regulation is partially mediated by the right insular cortex which often sustains damage in Alzheimer’s disease. Hypertensive demented patients have a steeper rate of cognitive decline than normotensive individuals (22).
Results of studies in individuals with mild cognitive impairment (MCI) appear less consistent for hypertension as a risk factor for persons with MCI progressing to dementia (23), (24), (25). Cardiovascular risk factors may be associated with the risk of developing MCI and the likelihood of transition from MCI into dementia; however, few studies have carefully examined this relationship (See Table 4).
Table 4. A Summary on Studies About the Role of Treating Hypertension in Preventing Dementia

<table>
<thead>
<tr>
<th>#</th>
<th>t</th>
<th>a</th>
<th>n</th>
<th>Treatment Effect on Dementia Risk and Cognition</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39 m</td>
<td>60+</td>
<td>2902</td>
<td>Reduction of 55% by treatment</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>6 m</td>
<td>69-</td>
<td>69</td>
<td>Lowering blood pressure did not lower cognition</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td>6 yrs</td>
<td>25-55</td>
<td>98</td>
<td>No adverse effect on cognition</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>22 m</td>
<td>65+</td>
<td>7046</td>
<td>Slight risk for dementia, probably vascular</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>6 yrs</td>
<td>55-</td>
<td>1979</td>
<td>Impaired cognition predicts poor compliance</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>5 yrs</td>
<td>60-</td>
<td>4736</td>
<td>No adverse effect from treating hypertension, unclear benefit on cognition</td>
<td>67</td>
</tr>
<tr>
<td>7</td>
<td>5 yrs</td>
<td>65-</td>
<td>1900</td>
<td>Antihypertensive treatment reduces odds of increased cognitive impairment by 38%</td>
<td>27</td>
</tr>
<tr>
<td>8</td>
<td>2 yrs</td>
<td>55-89</td>
<td>1993</td>
<td>Cognitive impairment may comply</td>
<td>54</td>
</tr>
<tr>
<td>9</td>
<td>3 yrs</td>
<td>65-</td>
<td>3308</td>
<td>AD with potassium-sparing diuretics</td>
<td>91</td>
</tr>
</tbody>
</table>

Meta-analyses are not available that examine the role of hypertension and cognition in longitudinal studies. A meta-analysis would be limited by the size and variability of the study populations as well as the techniques used to examine the relationship between hypertension and cognition. Substantial, longitudinal data suggests that early onset hypertension may be more damaging to cognitive function than late-life onset hypertension and treatment of early onset hypertension may diminish the risk for developing cognitive impairment in later life.

Brain infarction is a major complication that can result from hypertension and cardiovascular disease. Stroke substantially increases the risk for dementia in persons over the age of 65 (29), (30). Twenty percent of all older individuals have silent strokes which are most commonly lacunar infarcts in the basal ganglia (80%). This often unrecognized cerebrovascular disease doubles the risk for developing dementia in later life (31). Stroke risk factors include hypertension, atherosclerotic vascular disease, and elevated homocysteine.

C. Cognitive Effects of Pharmacological Interventions for Hypertension

Antihypertensive therapy may reduce the risk of cognitive decline in persons with chronic hypertension (26), (27) and treatment should not worsen cognitive function. No specific class of antihypertensive medication is consistently identified as more beneficial to cognition (See Table 4), (32), (33), (34). The first step in reducing hypertensive risk factors for cognitive decline is adequate, safe control of hypertension. Sustained compliance by the demented patient may become problematic, as dementia increases the likelihood of non-compliance (35), (36). Neurodegenerative changes such as senile plaques and neurofibrillary tangles begin to develop in some persons over age 50 and aggressive cardiovascular preventive interventions could be reviewed at this point in the patient’s life. Protection of left ventricular function and reduction of atherosclerotic risk factors would appear prudent for cognitive as well as cardiac health. Appropriate control of homocysteine in all age groups may diminish the risk of cognitive decline. Long-term folic acid and B-Complex vitamin supplementation appear to reduce the homocysteine level in many older individuals. Demented persons receiving appropriate antihypertensive therapy may have enhanced benefit.
Older persons with atrial fibrillation have increased risk of cognitive decline, as well as stroke and white matter damage (37), (38), (39). The cognitive benefit of prophylactic anticoagulants or anti-arrhythmic agents in older persons with atrial fibrillation has not been adequately studied. Conventional wisdom suggests prudent but aggressive therapy of atrial fibrillation as protection of cognitive and neurological function (40). Demented persons treated with antihypertensive medications may have better response to cholinesterase inhibitor therapy (28).

The majority of studies that examine the role of statins in dementia suggest a protective effect in some individuals, although several studies dispute this beneficial effect (41). The beneficial effect of statins on cardiovascular function suggests a possible reduction of vascular burden in the brain (42). Other putative roles for statin therapy include the reduction of amyloid burden. The risk-benefit ratio for statins supports the aggressive use of these medications in persons with hyperlipidemia; however, the prophylactic use of these drugs in at-risk populations for dementia is not recommended (41). The prophylactic use of low dose aspirin therapy for cognition has not been adequately studied. Click here for additional information on the role of statin therapy and cognition – DETA 2513.91.

D. Neuropathological Correlates to Hypertension
The role of hypertension and cerebrovascular disease in the pathogenesis of dementia or age-related cognitive decline remains vague because neuropathologist lacks precise methodologies to quantitate the extent of vascular damage to the brain. Longitudinal studies suggest that brains from decedents with chronic hypertension exhibit increased Alzheimer’s pathology. Senile plaque counts in brains of non-demented older subjects correlate to severity of coronary artery stenosis by atherosclerosis (15), (16), (43), but not premortem cholesterol levels (89). Hypertensive individuals have diminished brain volume in comparison to normotensive and increased microscopic pathology, as well as increased numbers of white matter lucencies (21), (44), (45), (46), (47), (48), (49). White matter damage is present in brains of intact and demented elders but this damage may worsen cognition in Alzheimer patients (50).

Microscopic examination of white matter blood vessels in persons with chronic hypertension demonstrate thickening of vascular media and loss of brain parenchyma around the vessel along with evidence of old perivascular microscopic bleeding as detected by hemosiderin laden macrophages around arterioles (45), (46), (47), (17). This non-specific finding can be seen in other disorders that produce neuropsychiatric symptoms including Systemic Lupus Erythematosus. White matter blood vessels are susceptible to hypertensive injury because they have diminished pressure regulating capacity in comparison to arborizing blood vessels in the cerebral cortex. This hypertensive arteriolar damage is associated with lacunar or slit-like infarcts in the white matter as well as in the basal ganglia and thalamus. Small vessel disease in white matter may correlate with cognitive decline (51).

E. Conclusion about the Role of Chronic Hypertension on Cognition
Mild, chronic hypertension in midlife may produce greater cognitive morbidity in later life than similar elevations of blood pressure in the very old. Hypotension in the elderly person
may be as problematic as moderately severe hypertension. Severe hypertension appears problematic in all groups. A further confounding issue is the role of multiple cardiovascular risk factors. The vague, imprecise neuropathological definitions used to diagnose “vascular dementia” incorporate only discrete quantities of infarcted brain parenchyma despite the fact that diffuse white matter hypertensive small vessel disease can produce wide-spread injury (17). In fact, neuroscientists have no accurate method of measuring total vascular damage in the human brain.

3. The Role of Cerebrovascular Disease in Dementia

Most strokes are produced by extracranial cerebrovascular disease originating in the left ventricle of the heart, the carotid system or the Circle of Willis. Older individuals have a significantly increased risk for developing dementia following a stroke and efforts to reduce risk factors for stroke may reduce risk for cognitive decline (17). Individuals with low left ventricular ejection fraction and atrial fibrillation have increased risk for cognitive decline with aging (40), (52).

The role of atherogenic medical conditions, such as hyperlipidemia, in the pathogenesis of cognitive decline remains contradictory, as some studies dispute the relationship between dyslipidemia and dementia. The protective role of statin medications also remains unclear. Elevated homocysteine and decreased folic acid are known risk factors for accelerated atherosclerosis (55). Folic acid supplementation may reduce the serum level of homocysteine and benefit cognition through cerebral vascular benefits or other undetermined mechanisms (56), (57). Click here for more information about risk factors for atherosclerosis – DETA 2513.91).

Data from the Nun Study suggests that vascular pathology is an important benchmark for cognitive decline in aging members of well-characterized populations, such as the clergy (58). Individuals with microscopic features of Alzheimer’s disease may retain intellectual function into later life; however, those individuals with both Alzheimer pathology and vascular damage were more likely to demonstrate cognitive deficits before death. Mixed dementias often include both vascular damage and Alzheimer’s disease.

The concept of cognitive reserve remains controversial; however, the newest science supports this principle. Cognitive reserve may reflect redundancy of synapses, redundancy of strategic cognitive functions through interconnected neural networks or enhanced neural plasticity. Dementia may occur when the cumulative burden of brain damage exceeds a threshold value required to sustain normal intellectual function. Click here for more information about cognitive reserve – 2513.51. Vascular damage to the brain may occur through several mechanisms including direct loss of neurons, disruption of vascular permeability, damage to vital white matter pathways carrying ascending fibers, such as cholinergic systems or disruption of cortical to cortical pathways that run through the hemispheric white matter (17). The addition of vascular damage to Alzheimer pathology may accelerate the onset of intellectual loss.

4. The Role of Cardiac Disease and Bypass Surgery in Cognitive Decline

Severe left ventricular dysfunction as measured by low ejection fracture (below 30%) is correlated to poor cognitive function (52). Specific kinds of cardiac or peripheral vascular disease, such as past myocardial infarction (90) or thickened carotid arteries may increase the
likelihood of cognitive decline in later life (51). Increased left ventricular mass is associated with diminished cognitive function over five years (93). The role of coronary artery bypass grafting (CABG) as a precipitant for cognitive decline in older persons is problematic for the primary care physician who may recommend bypass surgery. Multiple studies have suggested the adverse effect of CABG on the brain (59), (60), (61), (62); however, recent studies dispute this observation (53), (63). Post-operative functional brain imaging studies suggest diminished metabolic activity in persons undergoing CABG procedure, although obvious variables such as pump time, clamp time and gender do not seem to impact cognition. Post-operative delirium continues to be a major issue and these symptoms may persist for up to six months. CABG surgery can sustain left ventricular function and theoretically reduce other risk factors associated with dementia. The clinician must weigh risk benefits to each patient comparing the severity of cardiac morbidity to cognitive and functional status. Available data will not provide guidance for which patients might suffer greater cognitive loss following CABG surgery.

5. Future Directions for Crafting Preventive Recommendations on Vascular Risk Factors and Cognition

A prospective study that randomizes hypertensive individuals into treated versus non-treated groups to assess the impact of long-term antihypertensive therapy on cognitive decline will not be done for ethical and legal issues. Available data suggests diminished risk for dementia with treatment by potassium sparing diuretics (91) and others (88). The best available science indicates that midlife choices determine later life cardiovascular, cerebrovascular, and cognitive wellness. Hypertension, heart disease or metabolic syndromes are linked to cognitive decline; providing additional incentives to patients for compliance with medications and lifestyle changes (67). The potential impact of a cerebrovascular fitness program on the cognitive function for individuals over the age of 65 is unclear, although conventional, clinical wisdom would encourage the use of these interventions in persons of all age groups.

The concept of a “brain screen” has been proposed that includes prospective assessment of vascular risk factors in the older patient that may identify a substantial yield of disorders that respond to therapy (65). The role of preventive interventions in older persons remains unclear; however, conventional wisdom suggests that cerebrovascular risk reduction will likely benefit middle age and older individuals (92).
### Table 5. The Possible Role Of Cardiovascular Preventive Interventions In Midlife And Later Life For Dementia

<table>
<thead>
<tr>
<th>Intervention</th>
<th>40-60 Midlife</th>
<th>&gt;60 Older</th>
<th>Recommendation to Clinician</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Weight Control</td>
<td>Obesity correlated to cognitive decline</td>
<td>Unclear</td>
<td>Weight management in midlife</td>
<td>9</td>
</tr>
</tbody>
</table>
| 2. Control HBP                | Correlated to later cognitive decline | Unclear, except for severe HBP | 1. control all severe HBP  
2. \(\downarrow\) BP in midlife to \(\downarrow\) risk | 78, 26, 82, 88, 91 |
| 3. Statin Therapy             | Unclear but probably beneficial | Unclear | Treat dyslipidemia                                       | 41    |
| 4. Reduce Plasma Homocysteine | Correlated to \(\downarrow\) cognitive function in late life | Correlated to dementia | Vitamin supplementation                                   | 83, 84, 85 |
| 5. Exercise Program           | Correlated to \(\downarrow\) CV disease and \(\downarrow\) dementia | Correlated to dementia | Promote regular exercise                                  | 86    |

HBP – hypertension  
CV-cardiovascular

Recommendations to the Primary Care Providers

1. Monitor BP and treat hypertension as per published national guidelines.
2. Educate patients that cardiovascular fitness protects the aging brain.
3. Monitor for the metabolic syndrome and treat each component.
4. Maximize ejection fraction to optimize cognitive function.
5. Screen cognitive function for all bypass candidates.
6. Empower patients to control their cognitive aging by managing vascular risk factors.
7. Use dementia risk reduction as another compliance tool for medications, diet, and health behaviors.
References


Physician Fact Sheet About The Potential Role Of Cardiovascular Disease In The Development Of Dementia in Later Life

1. Individuals with untreated or under-treated hypertension during midlife may have increased risk of dementia in later life.

2. Individuals with untreated or under-treated hypertension during midlife may have diminished cognitive function in later life even in the absence of dementia.

3. Midlife obesity may increase the likelihood of late-life dementia.

4. The “metabolic” syndrome includes hypertension, dyslipidemia, obesity, and Type-II diabetes.

5. The metabolic syndrome in midlife is a risk factor for dementia in later life.

6. Midlife diabetes is a risk factor for cognitive decline and depression in later life.

   7. Stroke is a significant risk factor for dementia in later life.

   8. Elevated serum homocysteine is a risk factor for dementia.

9. Cardiac damage with low ejection fraction and left ventricular hypertrophy are risk factors for cognitive loss in later life.

10. Untreated atrial fibrillation may be a risk factor for dementia in older persons.

11. Available research methodologies cannot accurately quantitate the severity of vascular damage in the aged human brain.

12. Physicians can encourage long-term cardiovascular risk factor reduction and prevention of metabolic syndromes by linking these disorders to risks for dementia in later life.
How does high blood pressure increase my risk for developing dementia?

Your brain consists of 13 to 19 billion brain cells that require a continuous supply of oxygen and nutrients. Any health problem that disrupts the supply of essential nutrients to the brain may damage or kill brain cells. A rich network of blood vessels exists in the brain to assure a proper flow of blood. A stroke occurs when blockage of a big or small blood vessel stops the flow of essential nutrients and kills brain tissue.

Untreated or unrecognized high blood pressure in middle life (between the ages of 40 and 65) may increase the risk for losing intellectual function in later life. High blood pressure damages the brain by: 1) damaging the heart that pumps blood to the brain, 2) damaging blood vessels in the brain, and 3) producing bleeding in the brain. Measurement of blood pressure produces two numbers -- the systolic or top number and diastolic or bottom number, for example, a normal systolic/diastolic is 120/70. A normal systolic number (top number) should not exceed 140, and the diastolic number (bottom number) should be less than 90, for example 130/85.

Increased blood pressure can increase the work of the heart and causes heart damage. A damaged heart cannot pump properly and provide adequate nutrients to the brain. Untreated high blood pressure damages blood vessels in the brain, causing them to leak or become blocked. Thousands of tiny leaks or blockages can damage a great deal of brain tissue adjacent to the vessels. Blood vessels weakened by high blood pressure in the brain can burst and produce bleeding directly into the brain tissue and a stroke. Most brain damage cannot be seen with the naked eye or with brain scans. This damage can be identified at death by examining the brain with a microscope.

The risk for brain damage produced by chronic or severe high blood pressure can be reduced through medications. Antihypertensive treatment includes medications for high blood pressure that can protect blood vessels in the body and the brain with relatively few side effects to the patient. Diet and exercise also help lower blood pressure.

High blood pressure is a serious and sometimes dangerous threat to your brain function and your intellect. You and your doctor must work hard to keep your blood pressure completely into the normal range for your entire life. Medication can make your blood pressure normal, as well as protect the heart and blood vessels that are essential to proper brain function. CLICK HERE FOR MORE INFORMATION – 2513.11
PRACTICAL RECOMMENDATIONS FOR PROTECTING BLOOD VESSELS IN YOUR BRAIN

1. Get your blood pressure checked every 4 to 6 months over age 40.
   
   2. Talk with your doctor about high blood pressure.
   
   3. Control your weight and diet.
   
4. If you have high blood pressure, take your medicine as prescribed by your doctor.
   
5. Regular exercise and weight reduction may help lower blood pressure.
   
6. People of African American heritage have a higher risk for high blood pressure and heart disease.
   
   7. Exercise at least four times per week.
   
8. Talk with your doctor if your blood pressure medicine causes side effects, like dizziness, fatigue or problems with sex.
   
   9. Follow your doctor’s recommendations if you have a heart condition that requires other medicines like blood thinners, or drugs that control heart beats.
   
10. Always talk with your doctor before you stop or reduce your heart medicine.
2. ALCOHOL
2. PROMOTE MODERATE ALCOHOL CONSUMPTION

Heavy, sustained alcohol consumption is the primary risk factor in the development of alcohol-induced dementia. Many (8%) of older persons are problem drinkers. Heavy alcohol consumption may cause dementia or worsen the symptoms of other dementias such as Alzheimer’s disease. Most (2/3) older problem drinkers go unrecognized by primary care doctors. Many will reduce drinking at one year if the primary care physician provides 15-minutes of education about health consequences of excessive alcohol consumption. Alcohol-induced brain disease in older persons is avoidable by screening and counseling.

Selected clinical laboratory abnormalities should trigger further investigation of drinking habits including unexplained falls or injuries, unexplained elevated mean corpuscular volume (MCV) in the results of a routine CBC, unexplained peripheral neuropathies or recent deterioration of health status. Sobriety and proper nutrition may allow some recovery of physical and intellectual function. The degree of end-organ damage such as liver, pancreas, etc., does not predict the severity of alcohol-induced brain damage. Alcohol-related nutritional deficiencies do not fully explain alcohol-induced dementia and a person can develop this syndrome even with normal dietary intake. Persons with dementias of other etiologies should avoid alcohol as this over-the-counter medication can produce confusion (Click here for references – 2513.23).

Recommendation

Older individuals should avoid consuming more than 1 oz. of alcohol per day. Vitamin supplementation including B- Complex and Thiamin helps the recovering alcoholic; however, sobriety is the most important intervention for problem-drinkers (FOR MORE INFORMATION, CLICK HERE). (6110), (6111), (6112)
Physician’s Guide To Talking With Older Persons About Drinking

1. Overview
Primary care physicians often encounter older patients who continue to drink in the latter years of their life. The growing older population will require physicians to focus more on geriatric substance abuse. Aging baby boomers may increase the rate of substance abuse treatment for elders by 70% (1). An alcoholic beverage can be part of a pleasurable social event for an older person. Research suggests that drinking small amounts of alcohol may provide certain health benefits; however, the details of these benefits remain unclear. The health problems produced by excessive drinking are clear. Individuals who consume a glass of wine on a regular basis may have some health benefit; however, regular excessive consumption of beer or distilled spirits produces an increased risk for dementia. A consumer fact sheet is attached to this clinical summary for office use by older patients. Alcohol use may contribute to medical problems in 10% of older patients (2), (3).

2. Distinguishing Normal Alcohol Consumption from Problem Drinking
Many older persons continue to drink past age 65 and some will drink at age 85. The community prevalence of alcoholism or problem drinking in persons over 60 ranges form 2% to 10%. Elderly alcoholics can be divided into two groups: 1) individuals with early onset, life-long drinking, and 2) individuals who begin drinking at a later age (4). Click here for more information about alcoholism in the elderly – (Substance Abuse in the Elderly).

The consumption of 1 oz. of alcohol, such as one bottle of beer, one glass of wine, one shot glass of hard liquor, on a daily basis is probably safe in most older, cognitively intact persons (See Table 1). Consumption of more than 35 drinks per week for men and 28 for women meets diagnostic criteria for pathological drinking that may produce alcohol-related dementia. Older persons with any form of dementia or neurological damage should avoid alcohol. Consumption of more than 14 drinks per week is a concern for the primary care clinician in all older individuals (5). Individuals consuming sedatives, sleeping pills, or other tranquilizers should avoid the consumption of alcohol. Alcohol can interact with many drugs and patients should discuss alcohol consumption with their pharmacist and physician. Alcohol should not be consumed for “health benefits” but rather as part of a social occasion. Solitary drinking should be discouraged in older persons. Older persons should not consume alcohol to help with sleep as this drug will actually disrupt sleep architecture and increase the risk of obstructive sleep apnea.

![Table 1]

<table>
<thead>
<tr>
<th>Classification</th>
<th>M</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Drinking</td>
<td>7-10</td>
<td>7</td>
</tr>
<tr>
<td>Moderate Drinking</td>
<td>14</td>
<td>7-14</td>
</tr>
<tr>
<td>Problem Drinking&lt;sup&gt;3&lt;/sup&gt;</td>
<td>35</td>
<td>28</td>
</tr>
</tbody>
</table>

1=drinks per week  3=sufficient, long-term

(See Table 1)
consumption to produce dementia

The CAGE Screening Instrument can be used to identify elders at risk for problem drinking using four simple questions (See Table 2). The Michigan Alcohol Screening Test may provide greater sensitivity and specificity but this instrument requires more time for computing (6), (7). Individuals who smoke are more likely to drink heavily. Routine, clinical laboratory values may suggest heavy alcohol consumption including elevated GGT (Gamma glutamyl transferase) and macrocytic indicies on blood count (8), (9), (10). Unexplained peripheral neuropathies or frequent falls may also result from alcohol abuse.

Table 2
The CAGE Screening Questionnaire for Possible Alcohol Abuse (6)

<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Have you ever felt you should Cut down on your drinking?</td>
<td>C</td>
</tr>
<tr>
<td>2.</td>
<td>Have people Annoyed you by criticizing your drinking?</td>
<td>A</td>
</tr>
<tr>
<td>3.</td>
<td>Have you every felt bad or Guilty about your drinking?</td>
<td>G</td>
</tr>
<tr>
<td>4.</td>
<td>Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (Eye opener)?</td>
<td>E</td>
</tr>
</tbody>
</table>

Scoring: Item responses on the CAGE are scored 0 for “no” and 1 for “yes” answers, with a higher score an indication of alcohol problems. A total score of 2 or greater is considered clinically significant.

3. Longitudinal Studies on the Impact of Alcohol Consumption and Cognitive Function
Several longitudinal studies have examined the relationship of alcohol consumption and cognitive decline for older individuals (See Table 3). No studies support drinking as a preventive intervention for cognitive function. Several studies suggest that individuals with moderate alcohol consumption have better cognitive function than abstinent individuals. All studies confirm the harmful effect of heavy drinking on cognition.
Doctors often overlook problem-drinking in older persons, as two-thirds remain undiagnosed in primary care (2). The solitary, elderly male with a serious mental illness and multiple health problems is at greatest risk for alcoholism and suicide. Physicians may detect alcoholism when an elderly patient develops withdrawal during hospitalization for a medical or surgical problem. Heavy consumption of alcohol in later life can produce many health problems by damaging heart, liver, pancreas, muscles, peripheral nerves, and brain (8), (9). Alcohol-induced dementia is one of the five leading causes of intellectual loss in older persons (7).

4. Physician Management of Alcohol Consumption in Older Patients

Individuals who drink more than 1 oz. of alcohol per day should discuss this drinking with their primary care doctor. Individuals who drink more than 2 oz. per day should attempt to reduce alcohol consumption or eliminate alcoholic beverages from their diet. People who drink 3 or more oz. of alcohol per day have a drinking problem that requires medical attention. Binge drinking is usually an indication of an alcohol abuse problem. Individuals with a past history of alcoholism or heavy drinking should be advised to strive for total sobriety.

Older persons are encouraged to drink responsibly and encourage their friends to do the same. Many doctors take a “live and let live” attitude with older problem drinkers. A few doctors will make statements such as “they are old; what does it matter;” however, it does matter greatly to the health and wellbeing of that older person. Some older problem drinkers will significantly reduce alcohol consumption for over one year when encouraged by physicians to cease drinking (See Table 4). Responsible drinking is part of successful aging.
Older individuals with alcohol addiction may require medical detoxification and long-term support through organizations such as Alcoholics Anonymous. Older patients who develop withdrawal during hospitalization for an unrelated health problem should not be discharged until the alcohol abuse is addressed (3), (4).

Doctors should provide clear encouragement for sobriety to any patient with evidence for end-organ damage such as liver disease, pancreatitis or neurological problems including ataxia or peripheral neuropathy. These types of damage are associated with alcoholic dementia and sobriety may avoid future brain damage (9).

Sobriety can produce clinical and radiographic improvement with alcoholic patients. Some individuals with alcohol-related dementia will regain some cognitive function with prolonged sobriety. Radiographic ventriculomegaly may also improve with cessation of drinking and cortical volume may slightly increase (5).

5. The Value of Brief, Educational Interventions by Physicians
Multiple studies have examined the role of brief physician interventions in reducing acute and long-term alcohol consumption. Most interventions consist of a 15-minute discussion between the doctor and patient about the health problems produced by problem drinking as identified by patient screening. Sobriety is measured by self-reporting, normalization of laboratory indicators, such as serum GGT or reduction of alcohol-related expenses. Many studies describe interventions that occur in outpatient primary care screenings (27). Multiple trials describe the impact of brief primary care screening and interventions (16) for reducing consumption, medical morbidity, hospital care, health care expenditures, and alcohol-related deaths (17). Most studies show a variable reduction in the rate of drinking, improvement of health problems, and reduction of mortality (26) (See Table 4 above).

6. Conclusion
Alcohol and substance abuse will increase in older patients with the aging baby boomers (1), (18). Alcohol abuse and alcohol-related dementia may become a growing problem in older
persons. Primary care physicians should screen and treat older persons with alcohol abuse to reduce the risk of cognitive damage, beginning with a 15-minute discussion about long-term health consequences of heavy alcohol consumption (28). Primary care physicians should encourage sobriety of minimal alcohol consumption in most or all older patients using the IMBIBE guidelines (See Table 5).

Table 5

IMBIBE

<table>
<thead>
<tr>
<th>Table 5. Recommendations for Primary Care Physicians About Alcohol Consumption by Older Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Identify at risk individuals.</td>
</tr>
<tr>
<td>2. Monitor for specific, abnormal neurological findings or laboratory values.</td>
</tr>
<tr>
<td>4. Inquire about drinking or use the CAGE</td>
</tr>
<tr>
<td>5. Brief education about alcohol-related diseases may reduce pathological drinking.</td>
</tr>
<tr>
<td>6. Encourage limited drinking or sobriety in elders who imbibe.</td>
</tr>
</tbody>
</table>

The role of alcohol consumption in dementia or preventing dementia

---

28 PRIMARY CARE MANUAL ON WELLNESS IN ELDERS
References:


PHYSICIAN FACT SHEET ON RESPONSIBLE DRINKING IN ELDERS

1. Physicians can safely accept patient consumption of 1 oz. of alcohol per day in any form with minimal end-organ damage.

2. About 8% of elders have a drinking problem and some will develop withdrawal during hospitalization for unrelated health problems.

3. Patients with excessive alcohol consumption are more likely to develop medical problems, such as hypertension, and complications, such as neuropathy or liver disease.

4. Some problem drinkers will maintain sobriety at one year if you provide basic advice to them about the health consequences of excessive drinking.

5. The CAGE alcoholism screening instrument requires approximately one minute for administration and is valid in older patients.

6. Alcohol can be a serious health hazard when consumed with benzodiazepines.

7. Alcohol is a poor hypnotic and may disrupt sleep.

8. All patients with cognitive impairment should be screened for drinking and encouraged to immediately cease consumption of all alcohol products.

9. Unexplained anemia, macrocytic indices, such as MCV>100, elevated GGT or peripheral neuropathy may be produced by excessive drinking.

10. Alcohol-induced cognitive loss may slowly improve with long-term sobriety.

11. Alcohol damages heart, peripheral nerve, liver, pancreas, skeletal muscle, and brain.

12. Your patients benefit from screening for alcohol abuse in elders and providing basic counseling for problem drinkers.
CONSUMER’S GUIDE TO SAFE DRINKING

Alcohol is a beverage and drug. Alcohol produces many pleasurable experiences including relaxation and a sense of wellbeing. Alcohol is highly addictive when consumed in large quantities over many years. Modest amounts of alcohol, such as one glass of wine, a beer, or one ounce of alcohol in a mixed drink may be slightly beneficial to some older people. Drinking more than two ounces of alcohol per day can produce harmful health effects to the brain, heart, liver, as well as sensation in the feet and legs of older person.

Alcohol is broken down by the body into many chemicals that is similar to a substance similar to formaldehyde, which is used to pickle organs. Large amounts of alcohol can damage your brain. Dementia can result from heavy long-term drinking over a period of years. Alcohol-induced dementia is one of the five most common causes of intellectual loss in the older person.

Older persons should drink in moderation or not at all. One ounce of alcohol per day may be beneficial to persons who are physically healthy. Two ounces of alcohol per day is the maximum that an older person should drink and more than two ounces per day can produce health problems.

Any person with memory difficulty over the age of 65 should stop drinking alcohol. Alcohol worsens confusion in the older person, even those who do not suffer from dementia. Regular consumption of alcohol is not part of a successful aging program and older people should not drink for the “health benefits of alcohol”. Older persons with normal intellectual function can continue to drink in moderation but they should alert their doctor that they are drinking alcohol to prevent potential interactions with medications. In general, red wine is probably the least likely to produce health problems when consumed in moderation. Occasional drinking in normal older individuals is most likely safe.
3. DEPRESSION
3. IDENTIFY AND TREAT DEPRESSION

Untreated or under-treated depression may increase the likelihood of medical and cognitive morbidity. Depressed elders are more likely to have cardiovascular disease, fatal outcomes from myocardial infarction, disability from heart disease, cerebrovascular accidents, poor medication compliance, and dementia. Depressed elders often conceal depressive symptoms and screening is necessary to identify at-risk individuals. Depressive anxiety is often treated with benzodiazepines that may worsen confusion. Suicide is common in elders, especially single males who live alone and drink heavily.

Depression produces significant psycho-physiological stress that results in excessive secretion of cortisol. High sustained circulating steroids may be neurotoxic; especially to the hippocampus which is damaged by Alzheimer’s disease. Most, i.e., up to 90%, depressed patients are improved with routine antidepressant therapy. Depression is linked to dementia at two levels. First, depressed patients can develop a dementia-like syndrome termed “pseudo-dementia”. Although the cognitive deficits are generally corrected with treatment of the depression, about 20% of these individuals will be demented at two years from Alzheimer’s or some other dementia. Second, depressed elders have increased life-time risks of developing dementia via molecular mechanisms that are poorly understood. (Click here for references – 2315.33).

Recommendation

Routinely screen for depression and treat elders until the patient achieves full symptom remission. Avoid long-term use of benzodiazepines, nightly use of sedative hypnotics for sleep, or the use of chronic, long half-life tranquilizers. (FOR MORE INFORMATION, CLICK HERE - 8000, 8002)
A Primary Care Guide To Understanding The Interaction Between Depression And Dementia

1. OVERVIEW

Primary care physicians often diagnose depression in adult patients and this disorder may produce memory dysfunction in some older patients. Depression is a risk factor for patient non-compliance with treatment for other medical problems, including hypertension and diabetes. The primary care physician can assure older patients that treatment of depression may protect physical and cognitive health.

Depression is a common disorder in the elderly and specific groups of individuals have greater risk for developing mood disorders including persons with stroke, Alzheimer’s disease, Parkinson’s disease and other neurodegenerative disorders (1), (2), (3), (4). Several key issues remain unanswered in the depression puzzle. First, do people with depression experience increased risks for developing dementia? Second, would treatment of depression earlier in life mitigate the risk of depression in later life? Third, is the neuropathological substrate that produces depression in later life similar to that of dementia? Fourth, is depression simply a preclinical manifestation of dementia? Finally, how does the neurobiology of depression enhance our understanding of the relationship between dementia and mood disorders? The complexity of these scientific questions is further complicated by the limited prospective data on depression and dementia (5).

2. LONGITUDINAL STUDIES OF DEPRESSION AND COGNITION

Few longitudinal studies define the relationship between midlife depression and later life dementia. Several studies suggest that individuals with a history of depression in midlife may experience greater risks for dementia in later life and the risk of dementia increases with the frequency of hospitalization to treat the mood disorder (42) (See Table 1). Numerous methodological problems exist in relating treatments to cognitive outcomes because depression may be caused by multiple neurological mechanisms and patients demonstrate variable adherence to treatment (3), (6).

People with mild cognitive impairment and dementia exhibit greater rates of depression than age-matched cognitively intact individuals (7). Depressive symptoms may precede the onset of cognitive decline by several years. Memory dysfunction associated with depression, sometimes termed “pseudodementia”, may be a significant red flag for future dementia, as about 20% of these individuals exhibit permanent cognitive loss even with complete remission of depressive symptoms (8), (9). Chronic depression may produce hippocampal volume reductions in younger persons with normal cognition (8). Repeated bouts of depression that produce hospitalization may increase the risk for late-life dementia by 13% for each hospitalization (42).
3. THE RELATIONSHIP OF DEPRESSION AND HEALTH STATUS

Depression can be linked to health status and chronic midlife depression increases the risk for hypertension (10) and morbidity from cardiac disease in later life (11). Depressed elders with cardiovascular disease, stroke, diabetes, or multiple other medical conditions exhibit worse outcomes than those individuals with normal mood. Prospective randomized studies have not been performed to measure the impact of treating depression versus placebo therapy on medical outcomes (12), (13), (14).

Depression in the setting of dementia increases the likelihood of psychiatric and behavioral disability. In contrast, treatment of depression in persons with dementia is safe and effective (1), (15).

4. NEUROPATHOLOGICAL SUBSTRATES FOR DEPRESSION AND DEMENTIA

Depression often occurs in persons with Alzheimer’s disease and diffuse Lewy body disease (16), (17), (18). The neuropathological substrate for depression in aging and dementia remains unclear (19). Serotonin is produced by neurons located in the midline of the brainstem in the structure referred to as the “Raphe nuclei”. Alzheimer’s patients with depression have increased densities of tangles in brain stem structures (20) and reduced numbers of neurons that produce norepinephrine and serotonin (46). A central component to depression in Alzheimer’s patients is apathy and anergy (21). Individuals with Alzheimer’s disease and depression demonstrate increased severity of microscopic damage in the prefrontal cortices that is linked to apathetic symptoms (22). Cortical and brain stem Lewy body counts do not appear related to depression (23). Many persons with late life onset dementia have Alzheimer’s disease neuropathology at death (24); however, neither the severity nor the distribution of cortical damage appears related to concurrent depressive symptoms (25). However, postmortem examination of hippocampi from individuals with AD and lifetime depression reveals higher densities of senile plaques and neurofibrillary tangles than non-depressed demented individuals (38).

---

Table 1

<table>
<thead>
<tr>
<th>#</th>
<th>n (study size)</th>
<th>Age of Subject</th>
<th>Duration of Study</th>
<th>Effect of depression on risk for dementia</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1070</td>
<td>60+</td>
<td>1-5 yrs</td>
<td>‡ risk (2.94)</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>1357</td>
<td>LS</td>
<td>40</td>
<td>X2 ‡ risk, independent of vascular risks</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>1366</td>
<td>65+</td>
<td>10</td>
<td>Minor ‡ risk - (1.28)</td>
<td>31</td>
</tr>
<tr>
<td>4</td>
<td>766</td>
<td>65+</td>
<td>5</td>
<td>Depressive symptoms predict AD</td>
<td>32</td>
</tr>
<tr>
<td>5</td>
<td>594</td>
<td>78.5</td>
<td>10</td>
<td>Predementia / depressive episode ‡ risk</td>
<td>33</td>
</tr>
<tr>
<td>6</td>
<td>3346</td>
<td>65-84</td>
<td>5</td>
<td>‡ risk @ 2yr (1.9) and 5 yrs (1.6)</td>
<td>34</td>
</tr>
<tr>
<td>7</td>
<td>114*</td>
<td>65</td>
<td>3</td>
<td>‡ risk (2.6) for MCI</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>5781</td>
<td>65+</td>
<td>4</td>
<td>‡ symptoms = ‡ risk</td>
<td>35</td>
</tr>
<tr>
<td>9</td>
<td>2812</td>
<td>65+</td>
<td>12 yrs</td>
<td>Depressive symptoms not related to onset of dementia</td>
<td>36</td>
</tr>
<tr>
<td>10</td>
<td>4046</td>
<td>50+</td>
<td>1-25 yrs</td>
<td>Depressive symptoms are risk factor for late dementia</td>
<td>37</td>
</tr>
<tr>
<td>11</td>
<td>2220</td>
<td>65+</td>
<td>6 yrs</td>
<td>‡ risk for MCI</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>LS = 40 year longitudinal study (odds ratio)</td>
<td>*Individuals with isolated amnestic syndromes at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2013.34 The effect of Depression on Developing Dementia
The role of vascular brain pathology in the pathogenesis of depression remains unclear. White matter damage in the frontal cortices as manifested by MRI abnormalities appears related to risks for depression and perhaps dementia (10). White matter hyperintensities are most likely produced by hypertensive small vessel disease in regions like the centrum semiovale.

5. LINKING THE NEUROBIOLOGY OF DEPRESSION TO SUCCESSFUL COGNITIVE AGING

The neurobiology of depression in humans has been related to dysfunction of ascending catecholaminergic systems and abnormalities in cerebral cortical regions linked to regulation of mood, including the orbitofrontal cortices, subgenual prefrontal cortex and portions of the cingulate cortex. Memory deficits produced by depression may be attributable to dysregulation of serotonergic and noradrenergic innervation of the human hippocampus. Rodent models of depression are limited by issues of experimental design. Rodent models that use persistent stress to produce symptoms of depression suggest that high circulating endogenous steroids alter dendritic connections and reduce the capacity of rodent neurons to reproduce (neurogenesis) (27). Human hippocampal neurons may retain the ability to regenerate; however, this data remains unclear. Antidepressant medications, mood stabilizing agents, such as lithium and electroshock therapy, enhance the ability of rodent neurons to reproduce. This rodent data suggests the possibility that depression may have a substantial impact on human neuronal plasticity and regeneration, while antidepressant therapy may enhance reparative or regenerative capacity in the human brain (27).

6. THERAPEUTIC CONSIDERATIONS

Treatment of depression in all adult age groups is usually safe, effective, and affordable (28), (29). Compliance remains a major problem in the treatment of depression as well as all other medical comorbidities (Click here for more information - DETA 2514.12). Treatment of depression may enhance the likelihood that other risk factors, such as psychosocial stimulation, management of hypertension, regular exercise, and others are optimally managed. Second and third generation antidepressants, such as selective serotonin reuptake inhibitors, are highly effective for older patients. Assessment and management of depression in mid and later life should be part of the primary care strategy for cognitive wellness. Prophylactic treatment of non-depressed individuals with antidepressant medications is not indicated for the prevention of dementia. Exercise training of elders may also reduce the risk of depression and dementia (43).

The role of treating depression or heart disease in the prevention of “vascular depression” remains unclear. Randomized controlled studies have not been performed to determine the benefit of blood pressure control in the reduction of risks for either depression or dementia. Such studies are unlikely as the consequence of untreated depression precludes withholding long-term antidepressant therapy. (Click here for additional on information on the role of vascular disease in depression or dementia – 2513.12).

7. RECOMMENDATION FOR PRIMARY CARE PHYSICIANS ON THE MANAGEMENT OF DEPRESSION IN OLDER PATIENTS

A randomized controlled longitudinal study will not be performed on the impact of treating depression as a preventive intervention for dementia in middle aged or older patients. Like
hypertension, depression is a serious health problem that physicians are obliged to treat in order to reduce the risk for suicide and associated health problems. A meta analysis of 20 studies in eight nations demonstrated an odds ratio of 2.02 linking midlife depression to late-life dementia (41). A reasonable interpretation of this data would suggest that aggressive management of depression in midlife may reduce morbidity and mortality in later life. A consensus opinion from the National Institute of Mental Health states that late life depression may represent an independent risk factor predisposing to dementing disorders, even when depressive symptoms occur more than ten years before the onset of dementia (5). Depression screening is now recommended as a component to the annual Medicare evaluation.

The appearance of depression in an older individual who has otherwise normal cognitive function increases the likelihood that that person will develop dementia later in life (5), (8). Depressive symptoms may not correlate to the rate of cognitive decline over time (39). These individuals should be monitored on a regular basis with cognitive testing. Aggressive management of other health problems, such as hypertension, atrial fibrillation, cardiovascular disease, etc., is warranted in these individuals. There is inadequate research data to advise patients about “increased risks for dementia” with depression and such statements can produce distress in many patients, especially those with a past history of depression. Rather, the clinician is encouraged to advise the patient of the beneficial effect of treating depression on physical health and cognitive fitness. This positive message encourages a sense of self-determination and motivates the patient towards proactive interventions that may enhance their long-term cognitive function.

RECOMMENDATIONS TO PRIMARY CARE PHYSICIANS
1. Screen older patients for depression on an annual basis.
2. Monitor cognitive function in older persons with a past history of depression.
3. Treat depression until the patient returns to baseline and sustain normal mood through antidepressant maintenance therapy.
4. Avoid chronic prescription of benzodiazepines in depressed elders.
5. Monitor compliance for antidepressant therapy.
References

42. Kessing LV, Andersen PK. Does the risk of developing dementia increase with the number of episodes in patients with depressive disorder and in patients with bipolar disorder? J Neurol Neurosurg Psychiatry 2004;75:1662-1666.
PHYSICIAN FACT SHEET ON DEPRESSION AS A RISK FACTOR FOR DEMENTIA

1. Depression is a common disorder in mid and later life.

2. Depression occurs more often in patients with neurodegenerative diseases including Alzheimer’s disease, stroke, Parkinson’s disease and others.

3. Depression may worsen health outcomes in older persons, including cardiovascular disease, cerebrovascular disease, and diabetes.

4. Persons with adult-onset depression demonstrate increased risks for late life dementia.

5. Persons with dementia or mild cognitive impairment have significantly increased risk for depression.

6. Rodent models for depression suggest that stress may reduce the reparative and regenerative capacity of neurons.

7. Treatment for depression in all age groups is simple, safe, and cost-effective.

8. Most antidepressant medications are effective for treating mid or later life depression.

9. Physicians should avoid alarming patients with a past history of depression by focusing on the beneficial effect of antidepressant therapy.

10. Insufficient data is available to advise patients that treating mid or late life depression reduces their risk of developing dementia.
Consumer’s Guide to Understanding the Health Consequences of Untreated Depression

How Can Untreated Depression Impact Health and Memory?
Depression is a common health problem in all age groups. Depression is a brain chemical disorder that causes significant stress and suffering for the patient. Chronic depression increases the likelihood of health problems such as heart disease, disability from stroke, and poor control of diabetes. Many older persons with depression also complain of memory problems. Chronic depression that begins in later life may be an early sign of dementia. The physical and mental stress produced by depression may hasten intellectual decline in some older persons. Untreated depression in older persons may produce memory problems that resemble dementia, but these memory problems may improve with medications. CLICK HERE FOR MORE INFORMATION – 2513.31

How Can We Treat Depression?
Medication treatment for depression is highly effective in all age groups. The treatment of depression may reduce or eliminate long-term health consequences produced by chronic depression. Medicines for depression are simple, non-addictive and similar to medicines for high blood pressure or other chronic diseases. Depression can cause anxiety (nervousness) in many patients and these individuals often receive tranquilizers called “benzodiazepines” (Valium, Librium, etc.). These tranquilizers are often addictive. Treating the depression with antidepressant medications will often reduce anxiety. Nerve pills or tranquilizers can sometimes worsen memory. Antidepressant medications are not addictive and sometimes help memory.

How Does Stigma Impact Treatment?
Many persons with depression refuse to seek treatment because of fear or embarrassment of being labeled “crazy”. Depression often causes patients to lose hope or faith that treatment can correct the problem. People who are depressed are not going crazy. If you suffer from depression, you should seek medical assistance. Depression is not caused by human failure anymore than high blood pressure or diabetes. If your friend is depressed, you should encourage them to seek treatment.
WHAT YOU CAN DO FOR DEPRESSION

1. Treat depression like any other health problem.

2. Tell your doctor when you feel depressed.

3. Take your medicines that your doctor prescribes for depression.

4. Don’t stop your medications for depression until you speak with your doctor.

5. Stay physically, emotionally and spiritually active; even when you want to stay home.

6. Avoid nerve pills and alcohol for nervousness.

7. Avoid sleeping pills unless prescribed by the doctor.

8. Don’t drink at night to help with your sleep.

9. Encourage your friends with depression to seek medical help.

10. **Remember:** Depression is a disorder of brain chemistries – not a weakness of the soul.
4. NUTRITION
4. ADVISE A HEALTHY DIET AND PRUDENT NUTRITIONAL SUPPLEMENTATION

Calorie restriction is the only dietary intervention that may slow aging. Severe restriction of dietary calories may reduce oxidative damage in humans and diminish the expression of age-related apoptotic genes in rodents. The severity of calorie restrictions necessary to slow aging also lowers the quality of life for most individuals and this method of longevity promotion is unreasonable for most humans. Several diets or nutritional supplements may reduce the risk of cognitive decline. A heart-healthy diet may reduce other risk factors associated with dementia.

Vitamin supplements may help reduce the risk for dementia. Elevated homocysteine levels may be produced by deficiencies of B-Complex vitamins and Folic acid. Minor elevations of homocysteine in older persons increase the risk for heart disease, cerebrovascular disease, and dementia. Folic acid and B-12 deficiencies are common in persons over the age of 65 where many deficient individuals show no evidence of neurological or hematological abnormalities. Folic acid and B-Complex vitamin supplementation is a simple, safe, cost-effective intervention that may lower homocysteine levels in older persons.

Individuals with low levels of Omega-3 Fatty Acids may be related to increased risk for dementia. Omega-3 supplementation has not been shown to prevent dementia; however, patients may benefit from consuming two helpings of fish per week.

Elders with low levels of natural antioxidants such as Beta Carotene and Vitamin E have increased risks for developing dementia. A standard dose of Vitamin E supplementation is reasonable in older persons not receiving potential interactive drugs, e.g., coumadin. Many other vitamins, minerals, and substances have been mentioned as possible neuro-protectants or precipitants for Alzheimer’s disease. For instance, aluminum has no proven role in the pathogenesis of Alzheimer’s disease despite considerable discussion in the lay press. (Click here for references – 2513.43).

Recommendation

Elders need a balanced diet with basic vitamin supplementation for Folic acid and B-Complex vitamins. Encourage a heart-healthy diet to protect cerebro-vasculature and cerebral perfusion. In general, a heart-healthy diet is probably brain-healthy. For more information, click here – 2513.41, 2513.411, 2513.45.
A Physician’s Guide to the Role of Nutrition and Diet in Successful Cognitive Aging

1. Introduction
Primary care physicians are often queried by older patients about the wisdom of vitamin supplementation and proper nutrition in maintaining normal intellectual function. The precise role of midlife or later-life nutrition in aging and dementia remains unclear, although individuals with reduced levels of natural antioxidants appear to experience increased age-related morbidity. The role of vitamins, minerals, dietary supplements, and herbal remedies also remains unclear (1). Physicians are often queried about the role of nutritional choices in intellectual function and aging. This segment outlines common nutritional issues where sufficient peer-reviewed data exists to make specific recommendations.

A three-step process can be used to determine a recommendation by a primary care clinician: 1) is the nutritional supplement safe at standard doses, 2) is there credible scientific evidence to suggest possible efficacy and, 3) is the supplement reasonably priced. Since nutritional supplements are not regulated by the FDA, patients cannot be sure of the product’s content, safety or efficacy.

2. Vitamin Supplementation As A Neuro-Protectant
Homocysteine is a thiol-containing amino acid produced by demethylation of methionine (2). In older persons, elevated serum levels of homocysteine are related to accelerated atherosclerosis, as well as increased risk for heart disease and stroke. The major cause of death in younger individuals with homocysteinuria produced by cystathionine β synthethase deficiency is atherosclerotic vascular disease. Elevation of serum homocysteine above 15 to 20 μmd/l predicts adverse cardiovascular outcomes and increased risk for cognitive decline with aging (3), (4), as well as increased plasma levels of β amyloid (5). Elevated homocysteine can be related to deficiencies of folic acid and B-complex vitamins. Folic acid deficiency and B-complex vitamin deficiencies are common in older individuals, including those without evidence of pernicious anemia. Low folate status as measured by red blood cell folate may be related to risk for dementia in all ethnic groups including Latinos (7). Chronic, low levels of folic acid, Vitamin B12 or B6 can produce symptoms of dementia (8), (9). Most diets that include some green, leafy vegetables, meats, and other “fortified” food staples contain sufficient folic acid and B-complex vitamins to achieve minimum daily requirement. A standard “daily” vitamin supplement for older individuals typically contains adequate folic acid and B-complex vitamins to achieve adequate supplementation. Measurement of serum B12 and folate may be predictive of homocysteine levels. Neither evaluation will predict the onset of dementia; however, elevated homocysteine is associated with increased risk for cognitive loss in elders, cerebrovascular disease and dementia in older persons. Elevated homocysteine in a diabetic patient increases the risk for cognitive decline beyond the risk produced by diabetes (13).

Homocysteine levels (tHcy) may be linked to risk for dementia via vascular disease or other mechanisms. Supplementation of folic acid in the 0.5mgm to 5mgm range reduces tHcy by 25% and the concurrent use of vitamin B12 in the 0.5mgm range reduced tHcy by an additional 7% (10), (11). Typical, clinical supplementation includes both Folic acid and B12
to prevent unrecognized B12 deficiency (12). Supplementation of dietary niacin may also provide some protection against AD (6).

Clinicians are encouraged to discuss routine “senior” vitamin supplementation with midlife or older patients to reduce the potential risk factor associated with elevated homocysteine. Randomized controlled prospective studies have not been performed to confirm the “protective” effect of vitamin supplementation and available data does not show clear protective benefit (11), (12). A single study suggests that individuals who have suffered an acute myocardial infarction may have slightly worse outcome with post infarction supplementation of folic acid and B12. The risk-benefit and cost/potential benefit ratios would support vitamin usage in middle aged and older patients (14), (15). (Click here for additional information about homocysteine and dementia – 2513.411).

3. **Antioxidants As Neuro-Protectants**

Antioxidant supplementation as a cognitive protectant remains a controversial issue. Several longitudinal studies fail to confirm a relationship between antioxidant consumption and dementia risk (1), (16), (17), (18). Others studies have linked levels of natural antioxidants, such as Vitamin E, C, and beta carotene to risk reduction and reduction of inflammatory markers such as C-reactive protein (19). A wide range of food stuffs, including red wines, contain natural antioxidants which may reduce organ damage produced by excessive production of free radicals. Vitamin E is a potent antioxidant that may slow progression of Alzheimer’s disease. Rodent models of Alzheimer’s disease demonstrate reduced amyloid load with chronic antioxidant therapy (15). The therapeutic value of Vitamin E supplementation is unclear; however, this vitamin can produce toxicity when taken in large continuous doses. A standard supplementation of 300 units per day is included in many vitamins; however, some clinicians will prescribe 1,000 units of Vitamin E per day in persons at risk for Alzheimer’s disease. The beneficial effect of long-term, high-dose Vitamin E supplementation in humans remains controversial. Individuals receiving coumadin should exercise great care and patients are recommended to discuss any Vitamin E supplement with their pharmacist to exclude drug-drug interactions. The use of other potential antioxidants, such as Gingko Biloba, is equally controversial. Insufficient data exists to recommend antioxidant therapy as a dementia prevention measure (32).

4. **Weight Control to Reduce Risk Factors for Dementia**

Mid-life obesity and Type II diabetes are linked to dementia in later life ([CLICK HERE FOR MORE INFORMATION-2513.91](#)). The precise mechanism by which obesity and diabetes contribute to cognitive decline in later life remains unclear; however, obesity appears linked to the metabolic syndrome (20), (21). “Weight reduction” diets do not appear to impact risk of dementia; in fact, individuals who consume large amounts of tofu may have greater risk of cognitive decline (19), (22). Long-term dietary control with maintenance of normal body mass is probably beneficial to later life cognitive function. Prospective randomized studies comparing obese to normal individuals will not be performed and clinicians must advise middle-aged patients based on best available data. Many middle-aged caregivers of persons with dementia can be encouraged to maintain normal weight as a possible protective intervention against metabolic syndrome and increased risk of cognitive decline in their later life.
5. The Role of Metals and Trace Elements in Dementia

A variety of trace elements or heavy metals have been linked to dementia or cognitive decline. Certain metals, such as lead, are neurotoxic and toxic levels in humans can produce cognitive loss. Aluminum is the metal that has received the greatest attention over time. Aluminum is found within neurofibrillary tangles and human aluminum toxicity can produce fibrillary masses within neurons. Dialysis dementia was produced by excessive amounts of aluminum in the dialysate.

There is no conclusive evidence that links aluminum toxicity to Alzheimer’s disease. Acute or chronic exposure to many toxic substances, such as lead, can produce intellectual deficits and many metals can be found within neurofibrillary tangles. Amyloid has high affinity for certain metals, such as Fe (Iron), Al (aluminum), and Zn (zinc), which may promote the generation of reactive oxygen species (23). Aluminum is readily absorbed through the gastrointestinal tract; however, there is no evidence that individuals receiving aluminum-based antacids have suffered greater rates of intellectual decline. Anecdotal reports of improved cognitive function with chelation are not corroborated by randomized controlled studies and this potentially dangerous procedure is not recommended for individuals unless specific defined toxic levels of metals are identified. Available evidence does not support cognitive enhancement by nutritional supplementation with vitamins and minerals beyond those routinely included in “senior vitamins”.

6. Nutritional Programs or Dietary Supplementation to Protect Cognition

Long-term consumption of typical “Mediterranean” diet that is rich in mono-saturated fatty acids may be protective against cognitive decline. A diet with low animal fat, but high fish and cereal consumption may be protective (33), (46). Features of the Mediterranean diet may reduce complications from the metabolic syndrome including reduction of markers of vascular inflammation such as reactive protein (CRP) (29). Trans-fatty acids are produced by the partial hydrogenation of vegetable oils that helps solidify the fat. These fats account for 2% to 3% of calories consumed in American diets, especially in “fast foods”. These artificial food substances increase vascular risk factors (34). Paradoxically, high tofu intake may be associated with increased risk for cognitive decline (22), (Table 1). Long-term consumption of diets that are high in fish content may diminish the risk for dementia (30), (31). High intake of unsaturated fatty acids in mid-life may reduce the long-term risk for Alzheimer’s disease in later life (49).
There is incomplete scientific evidence to prove a preventive or therapeutic effect of nutritional supplementation for older persons. Prospective randomized controlled studies have not been performed to examine the protective effect of these dietary supplements over decades. Many other herbal substances and nutritional supplements have been touted as possessing anti-aging, antioxidant or anti-Alzheimer benefits; however, these claims are not substantiated by randomized controlled studies.

Clinicians must distinguish a genuine preventive benefit from a placebo effect. Many psychotropic medication trials produce significant placebo effects in persons not receiving the active molecule. Many patients provide personal attestations that a specific combination of vitamins and dietary measures will substantially improve their intellectual vitality or sense of cognitive ability. Nationally advertised “memory enhancing supplements” are not shown to improve cognition or reverse cognitive loss through large scaled, randomized controlled studies. The active constituents for these products are often available in cheap, generic forms.

As long as the dietary programs do not produce other health problems and the supplements are not excessively expensive, the clinician can encourage the patient to continue those interventions which are perceived as beneficial. The secondary benefits to the patients beyond a possible placebo effect may include enhanced awareness of health maintenance and stress reduction produced by a sense of control and self-mastery.

7. Consumption of Alcohol as a Risk Factor for Dementia

A consumption of alcohol as an antioxidant or cognitive protectant is controversial and contradictory. Frenchmen who consume wine in moderation may have diminished risk of cognitive decline; however, these individuals may have other lifestyle features that are not captured by available research (48). Individuals with excessive alcohol consumption may sustain a wide range of health problems; however, moderate drinking is associated with slightly diminished risk for cognitive decline (CLICK HERE FOR MORE INFORMATION – 2513.2). Clinicians are not advised to encourage patients to commence drinking in later life as a health intervention. Heavy drinkers in all age groups should be encouraged to abstain or reduce alcohol consumption. Social drinkers can be advised that moderate drinking is acceptable within certain limits. Wine is probably the preferable

---

**Table 1. Studies on Dietary Supplements to Improve Memory or Prevent Dementia**

<table>
<thead>
<tr>
<th>Study</th>
<th>Molecule</th>
<th>Outcome</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta n=0</td>
<td>Omega 3 Fatty Acid</td>
<td>Inadequate Data</td>
<td>24</td>
</tr>
<tr>
<td>Meta n=12</td>
<td>Lecithin</td>
<td>Demonstrated no benefit</td>
<td>25</td>
</tr>
<tr>
<td>Meta n=11</td>
<td>AcetyL Carnitine</td>
<td>Not recommended</td>
<td>26</td>
</tr>
<tr>
<td>4 Studies</td>
<td>phosphatidylserine</td>
<td>Slight improvement with AAMI/Minimal data</td>
<td>27</td>
</tr>
<tr>
<td>1 Study</td>
<td>DHA</td>
<td>Not recommended</td>
<td>45</td>
</tr>
</tbody>
</table>

Meta – Meta analysis of available data

2513.44 Nutrition/homocysteine and folic acid
beverage for these individuals. For more information on alcohol consumption in the elderly, please see DETA 2513.21.

**Conclusion and Recommendation**

Primary care doctors should examine three issues in crafting dietary recommendations for older patients: 1) safety, 2) evidence for efficacy, and 3) financial tolerability. A balanced diet with one or two servings of fish per week and basic vitamin supplementation is probably beneficial to all middle-aged and older individuals (32), (33), (34), (46), (47), (50). Normal weight in middle age should be maintained by proper diet and regular exercise. Folic acid and B-complex vitamin supplementation may be helpful to reduce risk factors associated with elevated homocysteine levels (28) although caution may be required in persons who have suffered an acute myocardial infarction (35). Moderate alcohol consumption is acceptable (48). Patient handouts on weight, alcohol, and diet are available (Click here for handouts – 2513.25, 2513.45, 2513.45-1).

**Recommendations to Primary Care Clinicians**

1. Educate patients that nutritional behaviors in midlife may impact cognitive function in later life.
2. Encourage heart healthy diets with additional servings of fish and less red meat.
3. Advise patients to take a standard, daily vitamin with B-complex and folic acid.
4. Monitor patient’s weight, avoid central obesity, and provide nutritional advice.
5. Advise patients who drink alcohol to consume in moderation. Red wine is probably the best form of alcohol.
6. Advise patients to avoid extreme diets and maintain an active life with exercise.
References

A Clinician’s Guide To The Role Of Vitamin Supplementation In The Prevention Of Dementia

1. Overview
Vitamin supplementation can be an important issue to the patient and medical professionals. Middle-aged individuals often query primary care doctors about the role of nutritional supplements in the prevention of common disorders, such as vascular disease or dementia. Older individuals are often concerned about maintaining cognitive vitality. Primary care physicians may be queried about the role of homocysteine in the pathogenesis of vascular brain damage and Alzheimer’s disease. Specific vitamin supplementations can be recommended for folic acid and B-Complex vitamins.

2. Linking Vitamins to Neurobiology
Vitamin supplementation for the prevention of dementia can be conceptualized in two-part categories: those vitamins that provide a neuroprotectant effect and those that reduce vascular risk factors. Vitamin supplementation has not been demonstrated to promote neuronal synaptogenasis or neuronal plasticity. The neuroprotectant vitamins often use antioxidant pathways, while many vascular protectants are mediated through reduction of homocysteine levels.

Studies show that 1 to 2% of all respired oxygen may be converted into free radicals which can produce neurotoxic effects. Mitochondrial damage is implicated as a contributory factor in senescent brain dysfunction. Both Vitamin E and Vitamin C may have antioxidant effects. Beta Carotene may also reduce overall oxidative stress. Large doses of Vitamin E have been reported to slow the progress of Alzheimer’s disease; however, the value of long-term, high dose Vitamin E supplementation as a neuroprotectant is unproven.

4. Homocysteine and Brain Function
Numerous publications document the relationship of homocysteine to neurological disease (1). Homocysteine is a sulfur-containing amino acid that plays a major role in the metabolic processing of thiol compounds. High levels of homocysteine in children will accelerate atherosclerotic deposits in arteries. Homocystenuria is a genetic metabolic abnormality produced by a cystathionine β-synthethase deficiency (CSD). Cystathionine β synthethase deficiency can raise homocysteine levels above 200 micromoles per liter. The heterozygote state for CSD is estimated to occur in 1 to 2% of the population and produces mild elevation of homocysteine in the 20 to 30 micromolar per liter range (1). Homocysteine may also play an important role in other disorders, such as Parkinson’s disease (2).

In adults, moderate elevations of plasma homocysteine in the 15-20 micro-molar per liter range significantly enhance risk factors for vascular disease. Other additional risk factors, such as diabetes and hypertension, enhance the overall impact of the elevated homocysteine. Vitamin B12 is an integral part of the metabolic pathway that converts methionine into homocysteine. Excessive quantities of homocysteine contribute to the production of increased quantities of excessive reactive oxygen species and lipid peroxidation that result in vascular damage (1). Vitamin supplementation with folic acid, B12 and B6 is recommended...
for the reduction of serum levels of homocysteine. Depressed levels of vitamin B12 and folic acid are associated with cognitive loss and depression (3), (4).

Some estimates suggest that up to 10% of vascular disease risk in the general population is due to elevated homocysteine (1). A single study of B-complex and folic acid supplementation following acute myocardial infarction demonstrated worse cardiovascular outcomes (23). Homocysteine levels appear to remain stable through the first four decades of life; however, after age 70, they appear to rise sharply.

The role of elevated homocysteine and B-Complex vitamin or folic acid deficiencies may be linked or may be separate factors. The connection between cognitive function and vitamin deficiencies or elevated homocysteine may be related to vascular damage in the brain or other unknown CNS effects.

5. The Role Of Folic Acid And B12 In Vascular Disease
Numerous studies have examined the role of homocysteine to atherosclerotic vascular disease. In a meta analysis of 27 studies on homocysteine and 11 studies on folic acid, the authors concluded that elevations of five micromoles per liter increments of serum homocysteine increase the risk for coronary artery disease and high intake of folic acid reduces the risk for atherosclerotic vascular disease (5). Multiple studies demonstrate an inverse relationship between dietary intake of folate and consequent risk of stroke and cerebrovascular disease (6). Elevated levels of homocysteine are also related to the severity of white matter pathology in older persons (7). Overall, available data suggests that either elevated homocysteine or diminished folic acid will increase the risk for peripheral and cerebral vascular disease (See Table 1).

![Table 1. The Association of Homocysteine and Folic Acid to Vascular Disease and Dementia](image)

6. The Relationship of Homocysteine Levels and Cognitive Function
Multiple studies have examined the relationship between total homocysteine levels and the risk for cognitive loss or dementia with aging (See Table 2). Most studies support an inverse relationship between late life cognition and elevated homocysteine levels. The
studies suggest that levels above 14μm/l increase the risk of cognitive decline in a dose-dependent manner. The severity of elevation and duration of elevation may be related to the relative risk for producing dementia in an older individual (8).

The precise mechanism that produces increased risk for cognitive decline is unclear. Elevated homocysteine may increase synaptic damage in the aging brain by accelerating the rate of vascular damage through infarctions and microvascular pathology. Elevated homocysteine may relate to elevated levels of β amyloid in aging humans (2).

A likely explanation involves accelerated vascular damage to the brain with consequent reduction of synaptic reserve as the primary event. Other vascular risk factors, such as diabetes, may enhance risk factors for cognitive decline produced by homocysteine (9).

### 7. Therapeutic Approaches to Lowering Homocysteine in Middle-aged and Older Individuals

A meta analysis of 12 clinical trials that include over 1,000 research subjects demonstrated that folic acid supplementation in the range of 0.5 to 5mgm would reduce plasma homocysteine levels by approximately 25% (10). Additional supplementation with doses of vitamin B12 in the dose range of 0.5mgm per day produced an additional 7% reduction of serum homocysteine; however, additional vitamin B6 did not appear to have significant impact on these serum levels (10), (37), (38), (39). In older individuals with vascular risk factors, supplementation with both folic acid and vitamin B12 appears to lower homocysteine by approximately 5 micromoles per liter (11). Combined supplementation with folic acid and B12 appears to be recommended by many clinical researchers (12). The long-term beneficial effect of folic acid and B12 supplementation in the maintenance of cognitive function or slowing of decline in demented patients has not been confirmed because long-term prospective studies have not been performed. The relative risk of B12-folic acid supplementation to middle-aged and older individuals is low. Folic acid supplementation is
routinely provided during pregnancy because of the impact of folate on neural systems. Dietary supplementation should exceed 500 micrograms of folic acid to achieve the desired effect.

Routine screening for homocysteine levels has not been endorsed by national organizations; however, clinicians may choose to assess this potential blood marker in at-risk populations. The risk-benefit ratio for mid-life supplementation with folic acid and B-complex vitamins appears to be low for long-term vitamin supplementation in the general population with recommended doses of folic acid (0.5 to 1 mg) and vitamin B12 (5 mg daily). Vitamin B6 supplementation is usually provided in standard dietary supplements; however, insufficient data is available to support any neuroprotective effect of this dietary supplementation with this vitamin (13), (19). Deficiency of folic acid and B-complex vitamins adversely impacts cognition in Black and Latino elders suggesting little ethnic difference in this relationship (18), (20). Sufficient indirect evidence is available to recommend vitamin supplementation during middle years when homocysteine levels begin to rise.

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>ID</th>
<th>Dose</th>
<th>ND*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiamin</td>
<td>B1</td>
<td>1.5 mg</td>
<td>Y</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>B6</td>
<td>2 mg</td>
<td>Y</td>
</tr>
<tr>
<td>Cyanocobolamin</td>
<td>B12</td>
<td>0.5 mg</td>
<td>Y</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>B2</td>
<td>1.5 mg</td>
<td>?</td>
</tr>
<tr>
<td>Folic Acid</td>
<td>---</td>
<td>0.5 mg</td>
<td>Y</td>
</tr>
<tr>
<td>Alpha tocoheryl</td>
<td>E</td>
<td>300 IU</td>
<td>N</td>
</tr>
<tr>
<td>Niacin</td>
<td>---</td>
<td>20 mg</td>
<td>Y</td>
</tr>
</tbody>
</table>

*Neurological Disease Associated with Deficiency

Recommendations to the Primary Care Physician

1. Encourage middle-aged patients to take a standard “senior” vitamin that contains B-Complex vitamins and folic acid.
2. Recommend routine daily doses of Vitamin E, i.e., 300 IU per day contained in standard OTC vitamins.
3. Mega doses of vitamins are not shown to reduce the risk of dementia and may produce drug-drug interactions, as well as increased morbidity.
4. Encourage healthy diets that provide a balanced nutritional intake.
References
A Consumer’s Guide to Understanding the Role of Middle Life Obesity on Intellectual Function in Later Life

How does my weight at age 45 impact my brain at age 65?
Over 60% of Americans are overweight or obese in their middle-aged years. Our modern lifestyles provide lots of food and little time for regular exercise. Overweight, older people have five times the risk of people with normal weight for developing diabetes (sugar) and very overweight people have 28 times the risk (CLICK HERE FOR MORE INFORMATION – 2513.97). New studies show that a “spare tire” or obesity around the belt in mid life can increase the risk of many health problems in later life, including memory trouble. Significant obesity around the beltline is produced by fatty deposits under the skin and inside the body cavity that holds your organs, like the stomach, liver and bowel. These fatty deposits alter the manner in which our body produces and destroys insulin. Insulin in the blood stream can alter the activity and health of brain cells. The disruption of proper insulin balance may trigger signals for a body response of inflammation that may attack the brain. (CLICK HERE FOR MORE INFORMATION – 2513.95, 2513.96, 2514.15)

A spare tire may increase the risk for problems with cholesterol, triglycerides, high blood pressure, and other health problems that are bad for your brain. Persons with a strong family history for Alzheimer’s disease or dementia should work hard in their 30’s, 40’s, and 50’s to reduce health risks that may worsen memory function in their 60’s, 70’s, and 80’s.

Your brain is only as healthy as the body that carries it around. All age groups benefit from maintaining normal healthy weight and deflating the spare tire.

How can I reduce risk factors for dementia associated with body weight?
1. Monitor your weight.
2. Eat healthy.
3. Exercise daily for at least 30 minutes.
4. Talk to your doctor about weight control.
5. Remember: Your brain is as healthy as the body that holds it. (CLICK HERE FOR MORE INFORMATION – 2513.41, 2513.411)
Consumer’s Guide to Dietary Issues for the Prevention of Dementia

How does diet impact brain function?
A proper diet is essential to good health. Many different kinds of diets are promoted to the public; however, no specific diet is proven to reduce the risk for developing dementia. A heart-healthy diet is recommended for all individuals to reduce risk factors for obesity, hypertension, and to avoid membership in the metabolic club. Diets that provide sensible amounts of fish, fresh vegetables, and fruits are preferred over diets that include multiple servings of meats and fried foods. Moderate alcohol consumption that is limited to one or two drinks per night is strongly recommended if a person chooses to drink alcohol.

How does vitamin supplementation benefit the adult brain?
Vitamin supplementation may have two beneficial effects for the brain: first, vitamins may protect brain cells against harmful molecules that are normally produced in the brain called “free radicals”. Second, vitamin supplements may reduce damage to blood vessels that are essential proper brain function.

The body produces large quantities of toxic molecules that damage brain cells, called “free radicals”. Free radicals are super-charged molecules that often involve oxygen. Some substances such as Vitamin E or C may reduce the damage produced by free radicals. Nutritional supplements often advertise their ability to “scavenge free radicals” meaning that the supplement will clean out these toxic substances. The scientific evidence does not support the protective role of scavenger molecules such as Vitamin E or C in protecting the brain or reducing the risk of developing dementia. Modest doses of these vitamins are present in most supplements and persons who take a daily vitamin should be assured that they are receiving adequate amounts to meet nutritional guidelines.

Does aluminum or other metals cause Alzheimer’s disease?
Aluminum cookware or aluminum content in drinking water has not been shown to cause Alzheimer’s disease. There is no clear scientific link between aluminum and dementia. Herbal supplements have not been shown to reduce the risk for dementia based on available science.

How do antioxidants impact my risk for dementia?
Food substances that are rich in molecules called “antioxidants” may be beneficial to persons as they grow older. Free radicals are super-charged molecules that can damage brain tissue. Antioxidants can reduce the toxicity of free radicals. Consumers should consider taking a vitamin that contains the recommended daily allowances of Vitamin E and other nutrients called antioxidants which are food stuffs that reduce the level of toxic molecules.

Which vitamins are best at protecting my brain?
The B-Complex vitamins including B6 and B12 may help protect your brain. Folic acid may be beneficial to brain and blood vessels. A standard daily senior vitamin contains the recommended dose of these essential substances. Individuals should discuss vitamin usage with their doctor if they have recently had a heart attack.

How can I pick a healthy diet for my brain?
1. Eat a balanced diet with fruits and green vegetables.
2. Include at least two servings of baked or broiled fish in your weekly diet.
3. If you drink alcohol, consume moderate amounts (1 drink per day).
4. Take a standard daily senior vitamin.
6. Avoid large doses of vitamins or expensive, exotic diets.
5. EXERCISE
5. Encourage Exercise and Psychosocial Stimulation

Life-long, physical exercise and psychosocial stimulation promote successful aging. Midlife obesity and development of the metabolic syndrome may increase the risk for dementia in later life. Life-time learning, late-life intellectual stimulation, and enhanced leisure activity may reduce the risk of dementia. Novel intellectual tasks are probably better than over-learned tasks because novel stimuli may activate under-utilized neural networks. Rodent studies demonstrate that synaptogenesis is promoted by environmental stimulation. Regular exercise or environmental stimulation will reduce amyloid load in the brains of transgenic mice that serve as a model for Alzheimer’s disease. Lifetime intellectual achievement may enhance cerebral blood flow and promote synaptic reserve that enhances intellectual resilience.

Human synaptic plasticity persists into the eighth decade based on human hippocampal studies. Psychosocial and intellectual vitality may promote synaptogenesis in the aging brain. Although exercise produces numerous benefits to the person over 65, less than half of elders exercise on a regular basis and over half of elders are physically inactive. Many diseases of the elderly are actually produced by disuse or preventable diseases (Click here for references – 2513.53).

Recommendation

Physical exercise is beneficial to elders of all ages and improves cardiovascular fitness, mood, bone density, muscle strength, and sustained exercise may diminish the risk for developing dementia. Intellectual and spiritual activity may enhance cognitive reserve and reduce the risk for dementia (FOR MORE INFORMATION, CLICK HERE - 2513.51, 2513.55)

1. Clinical Overview
Primary care physicians are often asked to recommend behavioral changes that might improve an older person’s chance for successful aging. The primary care physician can use insights from clinical, basic science, and pathological research to recommend intellectual, physical, and psychosocial stimulation as part of their cognitive wellness program for middle aged and older patients. The definition of successful aging can be divided into three domains including physical, social, and psychocognitive (1). In one study, 20% of older individuals reported poor physical functioning, 40% reported problems with social function, and 36% were identified as having psychiatric or severe cognitive disability. Only 13% achieved optimal scores for high overall functioning and 10% met all criteria for successful aging. Although elders experience many types of physical, mental, and social stressors, the majority continue to endorse a sense of wellbeing. This sense of accomplishment can become a major support for the successful aging of an older person (1).

2. Defining Intellectual Reserve in Humans
The interplay between lifetime intellectual achievement and late life cognitive function has been scrutinized by numerous scientists. Recently, the concept of “brain reserve” has achieved greater validity in the scientific community (2), (3). Brain reserve implies that a patient has sufficient functional capacity or redundancy to compensate for brain injury of subclinical functional loss. Some scientist would argue that there are three types of human brain reserve: 1) the number of neurons and synapses or the sophistication of synaptic connectivity, as well as the resilience of neurotransmitters or trophic factors, 2) the number of backup cognitive strategies to solve specific types of neuropsychological tasks presented to elders, and 3) the quantity or speed of brain tissue loss with advancing age.

Several studies support the role of early life intellectual achievement on later life intellectual function (4), (5), (6), (7), (8). Early and mid life intellectual achievement may predict enhanced metabolic activity on brain imaging in later life (9), (10). The Nun Study was first to suggest that individuals with greater, early life intellectual achievement experienced a diminished risk for developing dementia, even when the brain demonstrated significant Alzheimer-type pathology (11), (12). Subsequent studies have examined the role of early life intellectual function and late life cognitive function. Childhood mental ability appears related to the risk of late-onset dementia (13), as well as enhanced late-life function (14). Other studies suggest that the rate of cognitive decline in later life may be dose-dependent upon the intensity of academic achievement in early life (15). Other variables related to late life cognitive function include the number of siblings and rural location of childhood that predicts socioeconomic strata (16). A similar phenomenon is seen in other types of diseases or conditions that may produce intellectual decline, including cognitive loss following coronary artery bypass surgery and risk for HIV-related dementia (17). About 10% of postmortem brains from intellectually normal individuals will demonstrate Alzheimer pathology at death. Individuals with higher academic achievements are less likely to demonstrate cognitive decline, even with Alzheimer’s pathology in the brain (39).
3. Animal Models for Intellectual Reserve

Animal models of early life intellectual achievement are difficult to interpret. Environmental or physical enrichment paradigms involve more complex activities than simple learning. Rodent environmental enhancement includes intellectual stimulation as well as opportunities for exercise. Animal models of environmental enrichment suggest enhanced neural production, glial proliferation, trophic factor production and enhancement of neurotransmitters (18). The brains of animals raised in enhanced environments demonstrate enhanced production of neurons in the hippocampus and accelerated production of dendrites and synapses in both the hippocampus and the occipital lobe. The production of glia and blood vessels also appear to be enhanced in these animal models. Environmental enrichment also appears to increase the levels of certain trophic factors such as nerve growth factors or brain derived neurotrophic factors as well as specific neurotransmitters such as serotonin or acetylcholine. Transgenic models of amyloid-producing mice appear to exhibit diminished quantities of brain amyloid and enhanced cognitive function when those animals are raised in enhanced environments.

4. Leisure Activities as Promoters of Cognitive Reserve in Older Persons

A surrogate activity for intellectual stimulation in elders is leisure activities. Passive intellectual activities, such as watching television, demonstrate no significant benefit on cognitive loss. Other stimulating late-life activities, such as writing letters or social interactions, appear to diminish the risk for cognitive decline in elders. One activity during any particular day of the week reduces this risk by 7%. A 63% diminished risk of cognitive decline is detected in those elders in the top third of late life intellectual activity (19). Numerous other studies suggest a similar positive impact of leisure activities on cognitive abilities inferring that other types of intellectual or emotional stimulation may preserve intellect with aging (19), (20), (21), (22). For instance, loneliness will almost double the risk of developing dementia in older persons (40).

Rodent models of environmental enrichment appear to benefit rodents subjected to a variety of other brain disorders to include stroke, trauma, and epilepsy. The mechanisms of environmental enhancement for rodent models of brain damage are similar to those seen with rodent aging brain, i.e., improving neural plasticity or neurogenesis (23), (24).

5. Physical Exercise as a Promoter of Cognitive Reserve in Older Persons

Long-term physical exercise appears to exert a protective effect against clinical symptoms of dementia in humans (41). Older individuals who exercise on a regular basis, such as three or more times per week, appear to have an enhanced sense of wellbeing and a diminished risk for developing cognitive decline in later life or a delay in onset of symptoms (35). Walking and bicycling appears to have many beneficial effects to these individuals when done on a daily basis for 30 minutes or more (26), (27), (33). Physical exercise reduces the impact of age-related neuronal reproduction (36).

Rodent models of high exercise environments suggest that physical stimulation promotes neurological resilience and enhancement of vascular networks in rat brain (23), (24). Transgenic rodent models with high levels of exercise demonstrate diminished amyloid load in the neocortex. The cerebral brain mechanism that diminishes brain amyloid content is unclear but appears linked to overall brain function within the affected mouse (25), (27), (28).
Late-life, human cognitive decline appears related to mid-life obesity (29) and perhaps the metabolic syndrome that includes obesity, insulin resistance, diabetes, and elevated lipids (30). Central obesity appears to be a risk factor for hypertension and excessive insulin secretion which may be harmful to long-term neurological function. Obesity is related to life-time exercise which may correlate with relative risks for developing dementia. CLICK HERE FOR ADDITIONAL INFORMATION ON THE METABOLIC SYNDROME – 2513.91

The newest scientific data suggests that the brain is a use-it or lose-it organ with regards to physical and intellectual stimulation (16). Newer data suggests that exercise and cognitive stimulation exert benefits beyond maintaining synaptic resilience. Long-term effects from stimulation may actually diminish disease-specific changes based in rodent models. This second benefit remains unsubstantiated in human models; however, this scientific assumption appears reasonable based on other information. Mechanisms of synaptic plasticity detected in rodent brain appear present in human brain based on human surgical specimens (31).

6. Impact of Cognitive Training on Age-Related Changes in Function or Brain Imaging
Cognitive training may slow age-related cognitive decline for over five years for individuals using computer-based, training systems that included ten sessions with four booster sessions (37). Functional imaging shows enhancement in markers of neuronal plasticity in the brains of aged individuals who engage in “cognitive conditioning” (38).

A variety of commercial and free cognitive activity programs are available to promote “mental gymnastics”. Programs conducted by the individual, in groups, and on-line show significant promise for improving cognition and promoting cognitive longevity.

Each person has individualized tastes for intellectual or social activity. The clinician should encourage selection of an appropriate intervention and continued participation. Novel intellectual activities are preferred to repetition of already over-learned tasks; for example, learning a new language or discovering the computer.

7. Possible Conclusions Based on Available Science about the Role of Education, Exercise and Psychosocial Factors on the Risk of Developing Late-life Dementia in Humans
Comprehensive, prospective studies have not been performed on the role of physical, intellectual or environmental stimulation in preventing dementia. These studies will not likely be performed because of technical obstacles. No intervention provides an insurance policy against the development of dementia, especially in those individuals with a high genetic risk for Alzheimer’s disease. The available studies in humans indicate that lifetime exercise enhances overall physical wellbeing, cardiovascular fitness and cognitive wellness. Three mechanisms might explain this benefit including: 1) enhanced angiogenesis in the brain, 2) enhanced synaptic reserve, and 3) diminished amyloid load. A second issue is the role of midlife obesity and hypertension that may reflect diminished exercise and the increased risk for dementia in those individuals who may suffer from metabolic syndrome.
The second “protective” issue is the role of lifetime intellectual achievement on risks for cognitive decline. Synaptic reserve, neuroplasticity, and perhaps other factors such as neurotransmission, trophic factor, and neurogenesis may be impacted by lifetime intellectual achievement. The role of late-life intellectual stimulation is less compelling than early and midlife intellectual achievement (42), (43), (44). The relationship of leisure activities or other forms of intellectual stimulation such as social interactions to diminished risk for dementia suggests several mechanisms including stress reduction and overall cognitive stimulation. These interventions are difficult to quantitate and therefore, the beneficial consequence of these activities are more difficult to define than other variables such as blood pressure or homocysteine levels.

The combined package of intellectual, physical, and social stimulation appears to be the optimal recommendation by primary care clinicians for patients in mid to later life.

**Recommendations to Primary Care Clinicians**
1. Encourage middle aged patients to develop a regular physical exercise schedule.
2. Encourage all age groups to maintain normal body weight to reduce risk of dementia in later life.
4. Promote social and intellectual activity in older patients.
5. Encourage participation in “mental gymnastic” programs that appeal to the individual.
6. Identify lonely elders and encourage social reconnection.
7. Screen for depression in lonely or isolated elders.
References


Primary Care Fact Sheet on the Impact of Lifetime Education, Physical Exercise and Psychosocial Stimulation on Intellectual Function

1. Most elders describe themselves as “well” despite physical, social or neuropsychiatric deficits.

2. Higher, early lifetime educational achievement is associated with a diminished risk for late life dementia.

3. Each older human may have individual cognitive reserves that might protect against cognitive decline.

4. Animals raised with environmental enrichment will show enhanced markers for neuronal vitality.

5. Animal models for amyloid production show that environmental enrichment will reduce amyloid load in the rodent brain.

6. Regular exercise may diminish the risk of cognitive decline in human elders.

7. Midlife obesity is a risk factor for late life dementia.

8. Passive intellectual activities, such as watching television, may have minimal protective benefits for the aging brain.

9. Social and leisure activities may be highly beneficial for cognitive protection in the older individual.

10. Available scientific data suggests that lifetime intellectual and physical activity may reduce the risk for dementia in later life or delay the onset of symptoms.
The Consumer’s Guide to Understanding the Role of Physical and Mental Exercise in Preventing Dementia

New studies show that people who exercise on a regular basis throughout life may reduce their risk of developing intellectual problems with aging. Walking, bicycling, and swimming all seem to provide physical and intellectual health benefits for persons in all groups. Regular exercise also improves the health of your heart and blood vessels in the brain. Regular exercise is part of your plan to deflate that spare tire of excess weight around your beltline. Research on humans and rats suggest that exercise may increase your brain’s ability to keep functioning in the face of damage caused by aging or dementia.

Your brain is like your body – you can “use it” or “lose it”. Regular brain exercise may strengthen your brain against memory disorders like Alzheimer’s disease. Life-long learning and new mental challenges are good for your brain. Begin by shutting off the television. Older persons should accept new intellectual challenges, such as learning to use a computer or studying a new language. Avoid the same routine day-in and day-out. Shake-up those brain connections by writing letters to old friends and meeting new people.

People of all age groups should exercise their brain and body on a daily basis. Everyone should exercise 30 to 60 minutes per day in midlife. Older persons with health problems may need to consult with their doctor about safe, appropriate exercise. Your brain is only as healthy as the body that carries it around. CLICK HERE FOR MORE INFORMATION – 2513.55-1).
The Consumer’s Guide to Memory Exercises

Getting The Big Picture
Your brain is a “use it” or “lose it” organ. You can increase the reserve of your brain by exercising your brain cells on a regular basis. Intellectual challenges, new learning and social interactions provide the best form of exercise.

Mental Exercise Is Like Physical Exercise
A person who simply lifts dumbbells as exercise will not have total body strength. Muscular strength training includes balanced exercises that work all your muscle groups. The same principles probably apply for your brain. Watching television is no better exercise for your brain than lying on the couch helps condition your body. Each person has different interest and mental skills. People should continue to learn new information and accept new mental challenges as they grow older. Cross-word puzzles, learning the computer, joining clubs for new social or intellectual activities, expanding your circle of friends, learning a new skill such as choir or gardening, and many other new intellectual challenges exercise more parts of your brain.

How Can I Increase My Brain Strength?

1. Maintain intellectual activities through life, such as reading, spiritual studies, politics or other subjects that interest you.

2. Learn something new every day.

3. Change the little things in your life on a daily basis, like going to a new store, walking a different route and others.

4. Develop new mental skills like using a computer, taking classes, developing new friends or social contacts.
6. SPIRITUALITY
6. Understanding the Role of Spiritual Vitality in Aging

Spirituality is an inherent human feature that is often manifested through religious activity. The measurement of religious activities can be quantitated; however, spirituality lacks an accurate metric. This potential inaccuracy of spirituality measurement limits the availability of scientific data; however, the consensus of researchers supports the finding that individuals with increased religious activities or self-described spirituality have reduced age-related morbidity.

Physicians must carefully weight their words when discussing matters of faith and religion with the patient. The relationship between cognition, spirituality, and religious activity remains unclear; however, the social and intellectual stimulation produced by faith-based activities probably provides a protective effect for human cognitive function.

Physicians are encouraged to define the benefit associated with active spiritual lives in the older individual. Such discussions must avoid judgmental statements or suggestions that the physician is proselytizing to a specific faith (Click here for references – 2513.63).

**Recommendation**

Active, spiritual lives are beneficial to middle-aged and older individuals. Physicians can encourage older individuals to engage in faith-based activities and encourage faith communities to maintain active contacts with older persons. The healthcare system should respect all spiritual attitudes including those that deny the need for spiritual activities. (For more information, click here – 2513.61)
A Primary Care Guide to Addressing Spirituality in Midlife or Older Persons as a Component to Successful Cognitive Aging

1. **Issues of Incorporating Faith Issues into Medical Practice**
   Physicians are often hesitant to discuss spiritual matters or religion with patients for ethical and personal reasons (1). Some physicians may perceive questions about religion or spirituality as intrusive or a violation of physician-patient relationship; however, recent trends in medical education have caused 70% of medical schools to include course work on spirituality in clinical practice (2). Physicians are trained to treat patients regardless of the patient’s ethnic or religious background. The lack of quantitative methodologies to measure spiritual or religious activity limits the value of correlative studies that compare health outcomes to “spirituality”. This lack of clinical data reduces certainty among physicians about any demonstrated beneficial effect from personal faith as professed by the patient. Some physicians may doubt the existence of a higher power and some may harbor negative feelings towards religious or spiritual beliefs, as well as organized worship (3).

2. **Defining The Measurement of Spirituality and Religion**
   Spirituality can be defined based on the HOPE paradigm. The HOPE spiritual assessment follows the acronym with “H” representing sources of hope or strength; “O” represents the role of organized religion; “P” represents personal spirituality and practices; and “E” depicts the effect on medical care and end of life decisions. Some longitudinal studies with specific diseases, such as HIV infection suggest that patient survival is related to frequency of prayer and inversely proportional to the patient’s judgmental attitudes (4). The intensity and quality of a patient’s spiritual life is difficult to measure (18).

   The measurement of religion and spirituality may not provide equal prediction for outcomes. Several studies indicate that greater spirituality but not greater religiosity are more likely to predict good health in an older individual (5), (6).

3. **The Link Between Spiritual and Physical Vitality in Older Persons**
   Spirituality appears correlated to health outcomes and quality of life in older individuals. For hospitalized older individuals, increased spirituality predicts fewer depressive episodes and better cognitive function (7), (8). Longitudinal studies suggest that increased lifetime organized religious activity may predict decreased likelihood for prolonged, utilization of long-term care services by the older patient. Likewise, the magnitude of intrinsic, self-described spirituality appears correlated to outcomes of health and pain management (9).

   Individuals with active, spiritual and religious lives demonstrate a diminished risk of developing depression in later life, as well as severe functional impairment produced by the psychiatric disability (10), (11), (19), (20). The relationship between spirituality, religion, and health outcomes may be related to stress coping and maintenance of mood. Individuals with active spiritual lives appear to enjoy diminished levels of stress and less evidence for depression producing better outcomes for chronic health problems or hospital care. The role
of formalized religious activity is less clear; however, some studies do support the relationship between organized activity and reduced long-term medical morbidity (12), (13).

4. **Conclusion About the Role of Spiritual Vitality in Maintaining Cognitive Vitality**

   Older individuals can become marginalized in spiritual communities. Pastors may not recognize the positive impact of spiritual activity on the quality of an elder’s life and longevity. No data exists to compare spiritual activity with risks for developing cognitive decline. Spirituality may enhance psychosocial function (22). Depression, chronic stress, and diminished activity are potential risk factors for cognitive decline in later life that may be mitigated by active, personal spirituality. (CLICK HERE FOR MORE INFORMATION – 2513.31, 2513.51). A growing body of medical literature defines the role of spirituality in clinical practice (14), (15), (16). Physicians are encouraged to promote spiritual and religious activity in those patients who have selected to achieve these internal goals. Each physician must determine their level of comfort in discussing this matter with mid-aged and older individuals. Physicians should avoid proselytizing or attempts at convincing patients who hold contrary beliefs (13). Older persons often serve as caregivers and spirituality improves their overall outcome (20) (21).

**Recommendations to Primary Care Physicians**

1. Recognize that any active spiritual life may promote successful aging.
2. Consider the individual spiritual needs of each patient.
3. Encourage an active spiritual life in appropriate patients.
4. Respect those patients who do not maintain or value an internal spiritual life.
5. Empower patients to expect that their spiritual community will include them in all aspects of a faith life.
References:


Physician Fact Sheet on
Addressing Spirituality in Middle Age or Older Persons as a
Component to Successful Cognitive Aging

1. Spirituality is an important component of psychosocial wellbeing for some elders.

2. Physicians can discuss the value of spirituality with patients who express an interest in this subject.

3. A patient’s active spirituality may improve their hospital outcomes.

4. Active spirituality may reduce the risk for depression during hospitalization.

5. An active spiritual life may improve quality of life at the end of life for some elders.

6. Physicians should avoid proselytizing with patients.

7. Most patients are receptive to a respectful discussion about their spiritual life.

8. Lonely elders have an increased risk for dementia.

9. Spiritual communities offer intellectual and social stimulation.

10. Doctors can encourage continued participation in spiritual activities as part of the “wellness program”.


PRC160578v2
The Consumer's Guide for Spirituality

The human spirit and soul are powerful forces in all people. Every human has a unique spiritual life despite the fact that scientists cannot measure or define this human feature. Human spiritual activity is often channeled through religious activity. People are capable of active spiritual lives even when they do not practice an organized religion.

Spiritual activity is important for the physical and mental wellbeing of a person. Spirituality does not go down in aging and often increases as the person gathers more knowledge and wisdom. Science shows that persons with active spiritual lives have better results from hospital care. Spirituality produces a powerful stimulation to the brain and body.

Scientists cannot measure spiritual energy and therefore no science proves that active spiritual lives protect the brain. Despite the scientific limitation, many scientists believe that an active spiritual life is part of an active intellectual life that promotes brain health in older age. Middle aged and older persons are encouraged to maintain an active mental and spiritual life throughout their entire life to promote wellness.
7. HORMONE REPLACEMENT THERAPY
7. The Value of Hormonal Replacement

**Hormone Replacement Therapy in Women.** Hormone replacement therapy (HRT) is a controversial intervention for post-menopausal women. Estrogen and progesterone are powerful, psychoactive substances with receptors located in the hippocampus and the basal forebrain. Women who undergo oophorectomy for other medical purposes during midlife demonstrate specific neuropsychological deficits that improve over time. Rodent models of transgenic mice indicate that estrogen levels may play some role in the deposition of amyloid within the brain.

The Agency for Health Care Quality and Research concluded that hormone replacement therapy was not proven to be beneficial for long-term cognitive function. The possibility remains for subgroups of aging women who benefit from HRT.

HRT has not been evaluated in other forms of dementia, especially vascular dementia and diffuse Lewy body disease. The slight female predilection for developing Alzheimer’s disease beyond age-adjusted rates of survival has not been linked to differences in hormonal content (Click here for references – 2315.73).

**Hormone Replacement Therapy in Men.** Multiple studies have examined the role of testosterone in the risk and pathogenesis of Alzheimer’s disease. Diminished levels of testosterone in men have been associated with increased risk for developing dementia in later life.

Testosterone supplementation may have potentially adverse effects, especially on the prostate gland. The risk-benefit ratio for long-term supplementation of testosterone in aging men has not been determined. Testosterone supplementation has not been proven to be protective or beneficial in patients with Alzheimer’s disease. Individuals undergoing testosterone supplementation for other medical or physiological reasons could theoretically experience some preventive benefit from this medication; however, supplementation is not recommended as a preventive intervention for older individuals, even with a family history of Alzheimer’s disease. The role of testosterone in other forms of dementia, such as vascular dementia or diffuse Lewy body disease is undetermined (Click here for references – 2315.73).

**Recommendation**

Post-menopausal women should be encouraged to have a thoughtful discussion with a women’s health specialist to discuss the beneficial effects and the potential risks of HRT. Testosterone supplementation for men is not recommended as a preventive intervention for dementia. HRT is not recommended as a routine preventive intervention for dementia in men or women. For more information click here – 2513.71, 2513.75.
Basic Facts for the Primary Care Physician on Hormone Replacement Therapy (HRT) as a Preventive Strategy for Dementia in Women and Men

1. Overview for Hormone Replacement Therapy in Women

Estrogen and progesterone are powerful, psychoactive substances with receptors located in the hippocampus and the basal forebrain. Some women who undergo oophorectomy for other medical purposes during midlife demonstrate transient neuropsychological deficits after surgical removal of the gonads. The relationship between endogenous estrogen levels and risk for cognitive decline in older women remains controversial (1), (2), (27). Transgenic rodent models of Alzheimer’s disease demonstrate that estrogen levels may play some role in the deposition of amyloid within the brain (2).

Hormone replacement therapy (HRT) to prevent senescent memory loss or functional decline is controversial. Many studies have identified cognitive benefits from these medications in postmenopausal women while others demonstrate no improvement (See Table 1). Serious health consequences are reported with HRT, such as increased risk for deep venous thrombosis, hemorrhagic stroke and others (3), (4). Potential beneficial effects from hormone replacement therapy include suppression of menopausal symptoms, e.g., hot flashes, as well as slowing of osteoporosis (5).

The interpretation of scientific studies on hormone replacement treatment is complicated by several issues. First, which kind of hormone preparation is best suited for cognitive protection and does that preparation produce excessive morbidity or mortality in at-risk individuals? Second, at what age does initiation of HRT provide optimal protection for dementia? Some studies suggest that early treatment is beneficial while others cannot draw specific conclusions on this matter. Third, how long should treatment continue? Some studies suggest that treatment limited to the perimenopausal period may provide the best benefit. Other studies cannot substantiate that observation. Fourth, are there subgroups of individuals who would benefit from hormone replacement treatment? For instance, does the presence of a strong family history of Alzheimer’s disease, APOE 4 alleles, hypertension, metabolic syndrome or other potential risk factors increase the likelihood that estrogen will provide beneficial results in women? Fifth, are some women at excessive risk for complications from HRT as a “dementia prevention”?
Table 1. A Summary of Recent Studies on the Role of Hormone Replacement Therapy on Cognitive Function

<table>
<thead>
<tr>
<th>No.</th>
<th>t</th>
<th>a</th>
<th>n</th>
<th>Hormone</th>
<th>Outcome from Replacement Therapy</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CS</td>
<td>65+</td>
<td>2816</td>
<td>Mixed</td>
<td>No change</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>42 yr.</td>
<td>65+</td>
<td>4894</td>
<td>Mixed</td>
<td>NC - dementia, few side effects</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>4 yr.</td>
<td>65+</td>
<td>13807</td>
<td>Mixed</td>
<td>No benefit for cognition</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>5 yr.</td>
<td>50+</td>
<td>103</td>
<td>Mixed</td>
<td>Possible benefit in verbal memory for non-demented women</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>CS</td>
<td>75+</td>
<td>3024</td>
<td>Mixed</td>
<td>No cognitive benefit</td>
<td>13</td>
</tr>
<tr>
<td>6</td>
<td>1 yrs</td>
<td>65+</td>
<td>4532</td>
<td>Mixed</td>
<td>Risk of dementia, NC-MCI</td>
<td>14</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>50+</td>
<td>472</td>
<td>ERT</td>
<td>Risk for AD</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>1-5</td>
<td>65+</td>
<td>1124</td>
<td>ERT</td>
<td>ERT delayed onset of dementia and decreased risk</td>
<td>16</td>
</tr>
</tbody>
</table>

b: study of duration
^ Matched Study, mixed variable - mixture of estrogen and progestin
NC - no change
CS - cross-sectional
a: age of entry
Mixed - estrogen and progestin of variable doses and mixture
ERT: estrogen replacement therapy

2. Longitudinal Studies
Over 30 studies have examined the role of estrogen levels, perimenopausal events, and hormone replacement therapy on the risk for developing dementia (6), (26). Multiple, longitudinal studies have failed to conclusively determine the role of HRT in the prevention of Alzheimer’s disease (See Table 1). The preponderance of recent data suggests that hormone replacement therapy does not provide a significant protective benefit to women. The Agency for Health Care Research and Quality examined this issue and concluded that hormone replacement therapy was not proven to be beneficial for long-term cognitive function (29). The possibility remains that responsive subgroups exist within populations of aging women who may benefit from HRT.

3. Potential Toxicity of HRT Therapy in Women
Potential toxicity of HRT includes cardiovascular, biliary disease and stroke. The effect of HRT on coronary artery disease (CAD) remains controversial; however, there may be a “protective” effect on heart function (3). Risk for breast cancer remains controversial (5). Increased rates of mortality are reported with some forms of HRT and some variable benefit on bone density (See Table 2), (3).

Table 2. Major Complication of HRT in Post-Menopausal Women (3), (5), (8)

<table>
<thead>
<tr>
<th>Potential Complication</th>
<th>Conventional Wisdom</th>
<th>Study Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>NC or SL^1</td>
<td>10 observation studies</td>
</tr>
<tr>
<td>Stroke</td>
<td>↑ Risk</td>
<td>Over 4 studies</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>Undetermined</td>
<td>Multiple conflicting studies</td>
</tr>
<tr>
<td>Deep Venous Thrombosis</td>
<td>↑ Risk</td>
<td>Multiple conflicting studies</td>
</tr>
</tbody>
</table>

NC – no change

2513.71 Hormone Replacement Therapy (HRT)
4. Clinical Recommendations

Although lower estradiol levels in older women may be related to decreased cognitive function in later life (27), physicians should not recommend HRT as a preventive intervention for Alzheimer’s disease or other types of dementia. The risk-benefit ratio for HRT exceeds the uncertain benefit from this intervention; however, women receiving HRT to suppress perimenopausal symptoms or prevent osteoporosis may enjoy a small cognitive benefit from the medication (5), (6), (7), (16).

The effect of HRT on the risk of developing other forms of dementia, especially vascular dementia and diffuse Lewy body disease has not been evaluated. The slightly increased risk among older females for developing Alzheimer’s disease beyond age-adjusted rate of survival has not been proven to depend on differences in hormonal content.

The identification of groups with specific sensitivity to hormone replacement therapy might enhance the therapeutic selection process and reduce the risk to patients. This type of selective targeting awaits further research on the dementias. Other variables such as exercise, or genetic features, such as APOE typing, may play some role in predicting outcomes from therapy.

Hormone Replacement Therapy in Men

1. Overview of HRT for Men

The use of testosterone in aging males has increased 500% since 1994 and 30% in the year from 2003 to 2004 (17). The probable risk to older patients for prescription of endogenous testosterone is low; however, the cognitive benefit has not been conclusively proven (17), (18).

Several studies have examined the role of testosterone on the risk and pathogenesis of Alzheimer’s disease (See Table 3). Male andropause is described as a potential cause of some age-related brain pathology. Diminished levels of testosterone in men have been associated with increased risk for developing dementia in later life. Dietary supplementation of testosterone in mice that are genetically altered to produce amyloid demonstrate diminished amyloid load in medicated rodents. Rodent studies suggest that testosterone may alter the production and metabolism of amyloid in the brains of transgenic mice (19), (23). Post mortem studies on older human subjects demonstrate higher densities of neurofibrillary tangles and micro-infarcts in persons with lower levels of free testosterone (28).

Testosterone supplementation has potentially adverse effects on the prostate gland, although this effect remains controversial. The risk-benefit ratio for long-term supplementation of testosterone in aging men has not been determined. Testosterone supplementation has not been proven to be protective or beneficial in patients with Alzheimer’s disease (24). Individuals undergoing testosterone supplementation for other medical or physiological reasons could theoretically experience some preventive benefit from this medication; however, supplementation is not recommended as a preventive intervention for older individuals, even with a family history of Alzheimer’s disease. The role of testosterone in
other forms of dementia, such as vascular dementia or diffuse Lewy body disease is undetermined (24).

2. The Use of Testosterone as a Neuroprotectant
The interpretation of available scientific data on the role of testosterone and cognition is complicated by several scientific obstacles. First, what dose and preparation of testosterone or combinations of male gonadal hormones are best suited to enhance cognitive function? Second, do all males respond to hormonal replacement or do specific hormone-sensitive subgroups exist that would benefit from targeted therapy? Third, what is the optimal age for initiation of therapy? Fourth, do specific disease markers, such as APOE 4 alleles or metabolic syndrome, exist that can predict at-risk group of males who benefit from testosterone therapy? Fifth, what are the long-term, i.e., 20 years, complications of testosterone supplementation on hormone-sensitive tissue such as the prostate gland? Clarification of specific groups of older individuals who are at risk for developing dementia and exhibit certain markers for hormonal sensitivity may provide targeted therapeutic interventions that enhance benefit and substantially reduce any long-term risk form hormone treatment.

Table 3
The Relationship of Testosterone Levels in Older Males and the Risk for Developing Dementia

<table>
<thead>
<tr>
<th>#</th>
<th>a</th>
<th>t</th>
<th>n</th>
<th>Outcome of Study</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65+</td>
<td>CS</td>
<td>310</td>
<td>↑ Serum testosterone predicts ↑ cognitive function</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>32+</td>
<td>19 yr</td>
<td>574</td>
<td>↑ Serum testosterone predicts ↑ risk of dementia</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>65+</td>
<td>CS</td>
<td>210</td>
<td>Low free testosterone is a predictive of AD</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>65+</td>
<td>PM</td>
<td>232</td>
<td>Testosterone related to ↑ NFT’s and ↑ micro-infarcts</td>
<td>28</td>
</tr>
</tbody>
</table>

Note: CS - cross-sectional study, t - duration of study, n - study size

2513.74 Hormone Replacement Therapy (HRT)

Recommendations for Primary Care Physicians

1. HRT for both men and women is an unproven intervention to slow aging or prevent dementia.
2. HRT is not recommended as a “dementia prevention” strategy for women but this treatment may benefit women who receive hormones for other specific clinical indications.
3. HRT is not recommended for older males as a form of dementia prevention therapy.
4. Future clinical research may produce specific guidelines for selection of patients and HRT preparation as well as treatment duration to reduce the risk of dementia.
References – Hormone Therapy


Physician Fact Sheet on Hormone Replacement Therapy (HRT) as a Protective Intervention for Dementia

1. Data on protective effect of HRT for dementia in men and women is conflicting.

2. HRT may increase risk of stroke and DVT in women.

3. Estrogen supplementation may diminish amyloid deposition in rodent models for Alzheimer’s disease.

4. Long-term HRT for women is not currently recommended as a preventive strategy for dementia.

5. Women who receive HRT for other reasons, such as menopausal symptoms, may enjoy a mild cognitive benefit.

6. Testosterone deficiency in aging may contribute to age-related physical senescent changes.

7. Many males presently receive exogenous testosterone for multiple reasons, including andropause.

8. Low testosterone in males may predict increased risk for memory loss.

9. Testosterone therapy is presently considered safe in older males.

10. Testosterone supplementation should not be provided as prevention for dementia in males.
The Consumer’s Guide To The Role Of Hormone Replacement Therapy In Growing Older With A Healthy Mind

1. **Can hormone therapy help an older woman reduce her risk for developing Alzheimer’s disease?**

   Young women make adult amounts of sex hormones such as estrogen and progesterone. During menopause, several hormone levels change in a woman’s body and estrogen levels drop after age 50. The loss of estrogen produces many symptoms of menopause. Replacement of estrogen and progesterone is referred to as HRT or hormone replacement therapy.

   The brains of all humans are sensitive to estrogen. These sex hormones work by sending signals and altering brain function in both men and women. These hormonal sensitivities explain some psychological alterations that occur during pregnancy and menopause.

   Beginning in 1990, scientists recognized that some women who take hormone replacement therapy during menopause seem to have less risk for developing dementia in later life. This observation caused more scientists to examine whether hormones can protect intellectual function and numerous additional studies examined different groups, different types of hormone replacement, and different kinds of side effects or complications from these medicines. Studies suggest that hormone treatment after menopause may increase the risk for stroke, blood clot, and several other complications in women who take hormones as compared to women who take no hormones. Scientist could not agree on whether women with hormone replacement therapy enjoy some protection from intellectual loss in later life. Hormone replacement therapy may protect older women against symptoms of menopause and may protect against osteoporosis (bone softening). Scientists cannot predict which women will benefit from the medication, at what age, in what strength, and for what length of time.

2. **What is the best recommendation for hormone replacement therapy in women?**

   The best recommendation for hormone treatment is that older women should have a careful, thoughtful discussion with a doctor who understands older women’s health. Hormone replacement treatment should not be prescribed as a prevention strategy for dementia; however, hormone treatment may be highly beneficial to some patients for other health problems, such as menopausal symptoms or osteoporosis. Any woman who receives hormone therapy should be monitored by their doctor and fully informed about potential complications, such as blood clots in the leg or the lung. Hormone replacement therapy in older women is safe and beneficial to many older women. Some women who receive hormone replacement treatment may also experience some protective effect against intellectual decline or dementia. For details of the scientific evidence that support this fact sheet, please see DETA 2513.71, entitled “Basic Facts For The Primary Care Physician On Hormone Replacement Therapy as a Preventive Strategy for Dementia in Women and Men”. Future research may help doctors identify women who should use hormone therapy to protect intellectual function over age 65.
**Recommendations:**

1. Women should discuss hormone replacement therapy (HRT) with a doctor who is an expert on this subject.
2. Hormone replacement therapy (HRT) is not recommended as a preventive intervention for dementia.
3. “Natural” hormones or herbs that are sold as food supplements do not prevent dementia.

**Does Male Hormone Replacement Therapy Help Protect the Brain of Older Men from Alzheimer’s Disease?**

While most persons know about menopause for women, men also undergo hormonal changes with aging referred to as “andropause”. Older men begin to experience diminished production of the male hormone called “testosterone”. Reduction of testosterone does not eliminate the male’s ability to reproduce; however, this change may cause other alterations, such as muscle loss or erectile difficulties.

Men can take testosterone pills to replace hormones lost through aging. Some studies suggest that the loss of testosterone in males may increase the risk for intellectual loss in later life. Scientific studies do not show that hormone replacement will protect an older man from developing Alzheimer’s disease or losing intellectual function. These studies will be performed over the next decade and should provide valuable information for the aging male population.

Hormone replacement therapy with testosterone appears to be relatively safe; however, more studies will be required to examine the long-term effect of testosterone on tissue that is sensitive to male hormones such as the prostate gland. Male hormone replacement therapy is not indicated for older individuals because its beneficial effect on intellect is unclear and the medications may have the potential for producing side effects.

Future research will clarify the role of testosterone in the aging process of males and possible clinical markers for men who might benefit from long-term hormone replacement therapy.

**Suggested Actions:**

1. Testosterone therapy for older men is not presently used to slow aging or prevent dementia.
2. Over-the-counter “male hormone supplements” are not shown to improve memory.
8. Anti-Inflammatory Medications
8. Anti-Inflammatory Medications as Dementia Retardants

Long-term use of non-steroidal anti-inflammatory drugs (NSAID’s) may protect against Alzheimer’s disease by diminishing inflammatory response to amyloid deposits. The brain’s intrinsic inflammatory response may contribute to damage produced by Alzheimer’s disease and other degenerative disorders. Inflammatory damage may be mediated through two mechanisms: 1) the immune response provoked by deposition of amyloid within brain parenchyma and 2) immune response to damaged blood vessels within the human cerebral cortex. Human senile plaques often contain microglial cells and other evidence of inflammatory responses. Alpha 1 chymotripsin may be contributory to the neurodegenerative process and this inflammatory protein is over-expressed in the brains of some patients with Alzheimer’s disease. Longitudinal studies demonstrate that elevated levels of C-reactive proteins are associated with cognitive decline and cerebrovascular or cardiovascular disease. These non-specific inflammatory molecules may contribute to some microvascular damage that occurs in the brains of patients with Alzheimer’s disease.

Several longitudinal studies suggest that older individuals who take non-steroidal inflammatory medication may have a diminished risk for cognitive decline. The impact of non-steroidal anti-inflammatories on individuals with mild cognitive impairment is largely unknown.

Non-steroidal anti-inflammatory medication can produce significant acute and long-term complications including gastrointestinal hemorrhage. Definitive randomized studies to determine the long-term cognitive benefits of NSAIDS in middle life have not been performed and these studies are unlikely to be undertaken. (Click here for references – 2315.83).

**Recommendation**

Available clinical evidence indicates that NSAIDS should not be used as a preventive intervention for the treatment of Alzheimer’s disease or mild cognitive impairment. Individuals receiving these medications for other reasons, such as arthritis, can be informed that a small beneficial effect may be provided from these drugs. For more information, click here – 2513.81, 2513.85
Physician Guide to Understanding the Role of Inflammation in the Loss of Cognitive Function or the Development of Dementia in Older Persons

1. Overview on Neuro-inflammation
Primary care physicians may be queried by older patients about the wisdom of taking anti-inflammatory medications to reduce the risk of dementia (1). Several lines of evidence suggest that abnormal inflammatory processes may contribute to cognitive decline and the pathogenesis of dementia (1). Some epidemiological studies suggest that individuals with long-term consumption of anti-inflammatory medications were less likely to develop dementia; however, meta analytic review does not support this linkage (2), (3). A second line of evidence suggests a relationship between elevated serum levels of inflammatory markers such as C-reactive protein or interleukin 6 and increased risk for cognitive decline. Subsequent evidence demonstrates neurochemical and microscopic brain abnormalities that support inflammatory damage in Alzheimer’s disease.

2. The relationship of inflammatory markers and cognitive decline
Multiple longitudinal studies have examined the relationship between circulating immunological markers and the risk for cognitive decline in elders. C-reactive protein is a nonspecific inflammatory marker associated with a variety of cardiovascular risk factors. Individuals with metabolic syndrome demonstrate elevated levels of C-reactive protein that correlate to severity of cardiovascular disease. Isolated elevation of C-reactive protein is associated with increased risk for cognitive decline (See Table 1). Likewise, elevated markers for interleukin 6 and alpha 1 chymotrypsin are also associated with cognitive decline in later life. Data is not consistent in all studies; however, the general trend indicates that elevated markers for systemic inflammation predict elevated risk for cognitive decline (8).

Table 1

<table>
<thead>
<tr>
<th>#</th>
<th>n</th>
<th>a</th>
<th>t</th>
<th>Finding</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>540</td>
<td>&gt;65</td>
<td>CS</td>
<td>Chronic low grade inflammation may ↑ age-related cognitive decline</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>3031</td>
<td>&gt;65</td>
<td>CS</td>
<td>Markers for IL6 and CRP may predict ⬇ cognitive function</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>1284</td>
<td>&gt;62</td>
<td>3yrs</td>
<td>Alpha 1 – antichymotrypsin is associated with cognitive decline but not IL6 or CRP</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>799</td>
<td>&gt;70</td>
<td>7 yrs</td>
<td>↑ IL6 may predict ⬇ cognitive function</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>290</td>
<td>55+</td>
<td>3 yrs</td>
<td>↑ IL6 = ↑ risk in African-Caribbeans</td>
<td>28</td>
</tr>
</tbody>
</table>

n = study size  a = age  IL6 = interleukin -6  CRP = C-reactive protein  CS = cross-sectional

3. Animal models for brain inflammation
Rodents that are genetically altered to produce excessive amounts of Aβeta 42 amyloid in their brain may exhibit a diminished amyloid load after pretreatment with anti-inflammatory medications, as well as diminished inflammatory markers such as IL6 (9), (10). Conversely, excessive amounts of glucocorticoids in aged macaque monkeys are related to increased levels of βeta 42 amyloid in comparison to levels of βeta 40 and this over-production of toxic amyloid may be mediated through alterations of the insulin degrading enzyme (11). Chronic administration of Ibuprofen reduces the density of amyloid plaque pathology in the mouse model of Alzheimer’s disease (10). Molecular biological studies from rodent models suggest that NSAIDs directly alter the amyloid pathway by reducing Aβeta 42 peptide levels; however, this effect does not appear dependent on cyclooxygenase (COX) activity (12).

4. Neuropathology and Inflammation
Inflammatory cells may be an integral part of the damage associated with senile plaques and amyloid deposits. The role of inflammation in neurofibrillary pathology is less well understood. Microglial cells are intrinsic brain inflammatory cells that may be activated by glycation of the APOE protein (7), (13). The limited pathological data on the density of senile plaque and tangles counts suggest no difference between brains of persons who took NSAIDs and those who took no anti-inflammatory medication; even in medicated persons with better cognitive function (14).

5. Potential Pharmacological Interventions to reduce Inflammatory Processes
Damage produced by inflammation in the brain might be reduced by multiple methods including: 1) reduction of the severity of metabolic syndrome, and 2) use of non-steroidal anti-inflammatories. Long-term, low dose use of NSAIDs may protect against cognitive decline (15), (16), (17). The overall efficacy of these medications is undetermined. Long-term use of NSAIDs carries significant risks for gastrointestinal bleeding (18), especially during acute initiation of the medication. Long-term use of COX 2 inhibitors may produce significant risk for cardiovascular complications (19). The long-term use of these medications as an anti-Alzheimer protectant is not proven (20); in fact, there is no proven method to reduce possible brain damage produced by pathological immune responses in the older human.

Understanding the efficacy of anti-inflammatory medication is limited by the absence of double-blind placebo controlled trials (21). The suggestion that NSAIDs may act independently of cyclooxygenase (COX) inhibition may explain poor results produced by clinical trials for naproxen, celecoxib and rofecoxib in clinical trials (1). The conventional wisdom suggests that Ibuprofen may provide the safest, most cost-effective intervention for individuals required to take anti-inflammatories (3).

6. The Role of the Metabolic Syndrome in Producing Inflammation
The metabolic syndrome will increase levels of inflammatory markers such as CRP in older persons. The metabolic syndrome and increased inflammatory markers are independent risk factors for cognitive loss. Management of the metabolic syndrome may reduce some component of the inflammatory response (24), (25), (26). CLICK HERE FOR MORE INFORMATION – 2513.91

Genes that control proteins involved with inflammatory response may be altered in AD. Other future pharmacologic interventions may target the production of these inflammatory proteins (29), (30).
Clinical Recommendations to Reduce Inflammatory-Mediated Brain Damage

The risk-benefit ratio weighs against recommending non-steroidal anti-inflammatory medication to reduce the risk for dementia in older persons. Clinicians can advise patients about two possible methods of reducing the risk for dementia produced by an abnormal systemic inflammatory response. First, passive measures such as reduction of risk factors for metabolic syndrome may provide secondary effects through reduction of risk for excessive production of inflammatory responses. A second direct anti-inflammatory effect may be mediated through the use of ibuprofen or aspirin. Low dose aspirin may also be protective for declining memory in individuals 75 years in age and older -- a mechanism that maybe mediated by its anti-platelet effect (15), (16), (17). The chronic use of non-steroidal anti-inflammatories may also delay the onset of other neurodegenerative diseases such as Parkinson’s disease (23). Patients who use NSAIDs for other medical problems, such as arthritis, may enjoy a slight cognitive benefit from this medication (27) if used chronically (22).

Other immunological interventions to reduce amyloid burden have produced inconsistent results. Active immunization against Aβ amyloid has not been shown to be effective in persons with Alzheimer’s disease. Prophylactic vaccination in at-risk individuals may be attempted when safe, effective vaccines are developed.

Recommendations to Primary Care Physicians

1. Encourage treatment of the metabolic syndrome to reduce the risk of abnormal systemic inflammatory responses.
2. Chronic use of NSAIDs for other indications may slightly reduce the risk for dementia.
3. Chronic NSAID use carries significant risk for toxicity.
4. Discourage the use of anti-inflammatory medications to reduce the risk for dementia.
References—Anti-inflammatory Medications

10. van Groen T, Kadish I. Transgenic AD model mice, effects of potential anti-AD treatments on inflammation and pathology.
Physician Fact Sheet On The Prescription Of Anti-Inflammatories As A Preventive Intervention For Intellectual Loss Or Dementia

1. Individuals who consume non-steroidal anti-inflammatories may have a slightly diminished, long-term risk of developing cognitive decline.

2. Ibuprofen may be beneficial while other medications, such as COX 2 inhibitors, may have less beneficial effect.

3. Individuals with metabolic syndrome may have enhanced, systemic markers for systemic inflammation.

4. Inflammatory responses may play a role in the production of age and disease-related brain changes.

5. Amyloid and senile plaque provoke inflammatory responses in the brain.

6. Anti-inflammatory medications may alter the production of A-beta amyloid 42 in the brain.

7. Steroids may increase A-beta 42 amyloid production or alter levels of insulin degrading enzyme.

8. Long-term use of anti-inflammatory medications can produce significant gastrointestinal and cardiovascular morbidity in selected older patients.

9. Anti-inflammatory medications, such as aspirin, may be beneficial in other degenerative diseases, such as Parkinson’s disease.

10. The weak, potential benefit of anti-inflammatory medications does not counter-balance the risk of long-term medication use as a preventive intervention for dementia.
Consumer Guide To The Role Of Anti-Inflammatory Medications In The Prevention Of Dementia

How does your immune system work in the brain?
Inflammation is a protective mechanism in the body to eliminate dangerous bacteria, viruses, tumor cells, and other potential threats to the health and wellbeing of our system. The body is designed to recognize itself through special markers that distinguish “self” from foreign organisms. Specialized cells in the blood stream and the tissue serve as the defense weapons in protecting the body. When the defense cells no longer recognize the body marker as friendly tissue, certain body parts may begin to self-destruct. Auto-immune disorders (“automatic” and “immune”), means that “defense” cells attack the body. Certain auto-immune disorders, such as Lupus Erythematosis, damage the brain. Abnormal immune responses can target brain cells, blood vessels, and outer coverings of nerve processes termed “myelin”. Multiple sclerosis is caused by the body attacking its own nerve coating or myelin.

The role of the immune system in Alzheimer disease and dementia
Scientists are studying the role of the body’s immune system in changes that occur with Alzheimer’s disease and other types of dementia. Medications that suppress some types of immune response may provide a very limited protective benefit against intellectual loss in later life.

People with Alzheimer’s disease and other types of dementia have evidence of abnormal inflammatory response in the brain. Abnormal blood factor and immune cells are present in damaged areas of the brain of persons with Alzheimer’s disease. This response may worsen damage produced by Alzheimer’s disease. Numerous studies examine the benefit of treating patients with Alzheimer’s disease with medicines that suppress the body’s response to the disease.

The role of anti-inflammatory medications in protecting against dementia
Certain drugs, called non-steroidal anti-inflammatory medications (NSAIDs) can block molecules associated with inflammatory response. All NSAIDs have side effects. Most of these drugs can irritate or damage the stomach, kidneys, and the heart.

The protection provided by chronic use of NSAIDs against dementia is small; however, the risk for side effects is substantial. Current treatment recommendations do not include long-term use of NSAIDs as prevention against dementia. Persons who take NSAIDs for other conditions, such as arthritis, may enjoy a secondary benefit by a slight reduction in the risk of developing dementia.

The role of inflammation in producing brain damage associated with Alzheimer’s disease and other dementias remain unclear to scientists. Active research is underway to improve our knowledge and develop treatment strategies as prevention and early intervention. CLICK HERE FOR MORE INFORMATION – 2513.81
9. The Metabolic Syndrome
9. Managing the Metabolic Syndrome

The metabolic syndrome is a clinical condition that affects 45% of older persons and includes central obesity, hypertension, dyslipidemia and elevated insulin resistance with Type II diabetes. Several components of the metabolic syndrome have been associated with increased risk of cognitive decline in later life. The relationship with hypertension, cardiovascular disease, and dementia is discussed in the cerebrovascular wellness segment.

Recent studies discuss lack of exercise and midlife obesity as risk factors for the development of dementia in later life. Newer data suggests that Type II diabetes may double the risk for dementia, although the precise mechanism for this connection is unclear. Increased peripheral resistance to insulin may expose the brain to elevated levels of insulin which can alter insulin sensitive receptors in the brain. Diabetes is a demonstrated risk factor for atherosclerotic cardiovascular and cerebrovascular disease. The role of dyslipidemia in the pathogenesis of Alzheimer’s disease is unclear despite the role of APO lipoprotein-E Type 4 as a risk factor for dementia.

The metabolic syndrome may alter amyloid metabolism, vascular pathology, systemic inflammatory responses or a combination of all the above. Although scientists cannot precisely explain the interaction of metabolic syndromes and dementia, clinicians are justified in linking long-term intellectual function to management of risk factors for metabolic syndrome including obesity, hypertension, and hyperlipidemia (Click here for references – 2315.93).

Recommendation

Physicians can advise midlife patients that the metabolic syndrome increases risk of cognitive decline in later life. Prophylactic statin use is not recommended for dementia prevention in persons with normal lipid levels. Advice about the potential “neuroprotective” effect may enhance compliance for weight management, blood pressure control and statin therapy for appropriate persons.

For more information, click here – 2513.91, 2513.95.
The Primary Care Guide To Understanding The Role Of The Metabolic Syndrome In Cognitive Decline Of Older Persons

1. Defining the Metabolic Syndrome

A Primary care practice often includes numerous patients who belong to “Club Metabolique”. Patients often want to achieve the health benefits of quitting a very non-exclusive, unhealthy club. The metabolic syndrome, previously termed “Syndrome X” or “insulin resistance syndrome” exists in 25% of the adult population (1). The metabolic syndrome includes central obesity, hypertension, dyslipidemia, and elevated insulin resistance with Type II diabetes and occurs in 40% of older persons. Several components of the metabolic syndrome are associated with increased risk of cognitive decline in later life (2). The relationship with hypertension, cardiovascular disease, and dementia is discussed in the cerebrovascular wellness segment (CLICK HERE FOR MORE INFORMATION - DETA 2513.11). New second and third generation antipsychotic medications may also produce metabolic syndrome in adults with no previous evidence for this condition. Routine monitoring is recommended for these patients (See Table 2). A patient handout on the price of the Metabolique Club membership is included in this packet - 2513.95, 2513.96.

The National Cholesterol Education Program III (NCEP) guidelines define metabolic syndrome as the existence of three of five risk factors identified in Table 1. These risk factors include obesity, low HDL-C levels, elevated triglycerides, systolic or diastolic hypertension and elevated fasting blood sugar levels. Some values are adjusted for male versus female. Ancillary features not included in the definition include evidence of chronic mild inflammation as seen with elevated serum levels of C-reactive protein, as well as enhanced oxidative stress, thrombophilia, and endothelial dysfunction (Click here for more information about inflammation and dementia – 2513.81). Each of these diagnostic features has specific available, safe, therapeutic interventions. Many of the ancillary features of the metabolic syndrome are identified as risk factors for the development of dementia and metabolic syndrome in later life is associated with Alzheimer’s disease (7).

2. Risk Factors for Metabolic Syndrome

The risk for metabolic syndrome increases with age and is enhanced in African American citizens, as well as those with less than a high school education (3). Menopause increases the risk for metabolic syndrome by 60%, as well as psychological stress that may increase
plasma cortisol levels (1). The risk for metabolic syndrome increases 23% per 10 pounds of weight gained in older persons; however, the overall risk is reduced with regular exercise. Elders with metabolic syndrome were more likely to have cognitive impairment, especially those with evidence of a systemic inflammatory marker such as creactive protein (4), (7). Metabolic syndrome is also identified as a significant risk factor for silent brain infarction in otherwise healthy persons (5).

Recent studies discuss lack of exercise and midlife obesity as risk factors for the development of dementia in later life (6), (8) (Click here for more information – 2513.45-1). Central obesity in midlife is a significant risk factor for metabolic syndrome (See Table 3). Obesity increases the likelihood of dementia, reduces life expectancy (See Table 4) and increases the risk for Type II diabetes, as well as cerebrovascular disease; however, the definition of obesity may be less stringent in the elderly than younger adults (26). Obesity and other risk factors for metabolic syndrome are common health problems in many nations and cultures (See Table 5).

Newer data suggests that Type II diabetes in older persons may be a risk factor for the development of dementia (9), although the precise mechanism for this connection is unclear (Click here for more information – 2514.31). Increased peripheral resistance to insulin may expose the brain to excessive levels of circulating insulin which can alter insulin sensitive receptors in the brain (10), (11), (12). Diabetes is a demonstrated risk factor for
atherosclerotic cardiovascular and cerebrovascular disease, as well as dementia. The role of
dyslipidemia in the pathogenesis of Alzheimer’s disease is unclear despite the fact that the
presence of APO- lipoprotein Type 4 alleles is a risk factor for dementia. Neither the levels
of total cholesterol nor high density lipoprotein in late life are consistently correlated to risk
of subsequent cognitive decline (13).

3. Understanding the Impact of Metabolic Syndrome on Cognitive Function in Later Life
The metabolic syndrome may alter risks for dementia based on a direct impact caused by
specific pathologies including: 1) deposition of amyloid, 2) acceleration of vascular
pathology, 3) accelerated production of neurofibrillary tangles, 4) enhanced inflammatory
response, or 5) a combination of all the above. Although scientists cannot precisely explain
the interaction of metabolic syndromes and dementia, clinicians are justified in linking long-
term intellectual function to management of risk factors for metabolic syndrome including
obesity, hypertension, and hyperlipidemia.

The protective effect of statin therapy remains controversial with multiple studies showing
protection (14), (15) and a few studies disputing this beneficial effect (16). Statins may
reduce cardiovascular morbidity and this benefit may protect cognition (17), (18), (Click here for more information about statin use and dementia – 2514.21). Prophylactic use of
statins in persons with normal lipid profiles is not recommended as a preventive intervention
(See Table 5).

Table 5. Conclusions About Metabolic Syndrome

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Independent Risk Factor for Dementia</th>
<th>Recommended Intervention</th>
<th>Exercise Improves</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Blood Sugar</td>
<td>Yes</td>
<td>BS, weight, meds</td>
<td>☑️</td>
</tr>
<tr>
<td>↑ Triglycerides</td>
<td>?</td>
<td>Diet, meds</td>
<td>☑️</td>
</tr>
<tr>
<td>Low LDL Cholesterol</td>
<td>?</td>
<td>Diet, meds</td>
<td>☑️</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>Meds</td>
<td>☑️</td>
</tr>
<tr>
<td>Obesity</td>
<td>Yes</td>
<td>Diet</td>
<td>☑️</td>
</tr>
</tbody>
</table>

Meds-appropriate medications Diet-dietary management

4. Treating Metabolic Syndrome in Adults
The metabolic syndrome is a collection of disorders that often produce disease that is greater
than the sum of the individual pathogenesis (27). Weight control, exercise and blood sugar
management are central features of management (18) (See Table 5). (Click here for more
information about on the role of diabetes in dementia – 2514.31).

Recommendations For Primary Care Physicians
1. Screen for metabolic syndrome in adults.
2. Promote exercise on a daily basis for all adults.
3. Encourage weight control as a component of cognitive wellness.
4. Treat each component of the syndrome to achieve maximum management.
5. Explain the potential impact of metabolic syndrome on cognitive function to the older
   patient.
REFERENCES FOR METABOLIC SYNDROME


Primary Care Fact Sheet on the Role of Metabolic Syndrome in Cognitive Decline in Older Persons

1. Older patients with metabolic syndrome are more likely to have cognitive impairment, especially with elevated systemic indicators for inflammation.

2. Metabolic syndrome includes at least three of the following: 1) central obesity, 2) hypertension, 3) elevated triglycerides, 4) low HDL cholesterol, and 5) increased fasting BS.

3. About 40% of older individuals meet criteria for metabolic syndrome.

4. Central obesity in midlife is a risk factor for dementia in later life.

5. Metabolic syndrome increases the likelihood of coronary artery disease.

6. The risk of metabolic syndrome increases 23% for each additional ten pounds of excess body weight.

7. Menopause produces a 60% increased risk for metabolic syndrome.

8. Metabolic syndrome is associated with silent brain infarctions in otherwise healthy individuals.


10. Controlling metabolic syndrome requires long-term compliance with medications, diet, exercise, and lifestyle.

11. Hypertension is a consistent risk factor for dementia.

12. Statins and antihypertensive medications may reduce risk for cognitive decline through multiple molecular mechanisms.
The Consumer’s Guide for Quitting the “Metabolic Club” or How I Beat the Metabolic Syndrome

Membership Benefits For The Metabolic Club
The metabolic syndrome is a medical term for a condition that is familiar to many middle-aged individuals. Persons with high blood pressure, high blood sugar, high triglyceride or cholesterol and central obesity, termed “a spare tire”, have what doctors called the “metabolic syndrome”. Persons who have three of these health problems qualify for membership in the metabolic club. Membership privileges include increased risks for heart attack, stroke, and dementia. The fatty tissue that produces the spare tire disturbs the body’s response to insulin causing other changes that may be harmful to your brain. These health problems each produce long-term effects in the brain; however, their combination together is more damaging than each alone. These health problems trigger immune responses that may further damage blood vessels, the heart, and the brain.

Quitting The Metabolic Club
Older individuals do not want to be the members in the metabolic club. The reduction of these risk factors is simple and provides multiple health benefits. Losing weight and reducing fatty tissue will improve the body’s response to insulin. Weight reduction helps with blood pressure. Regular exercise helps reduce weight and reduce blood pressure, as well as improving intellectual fitness (For additional information, See DETA 2513.51 on Exercise and Intellectual Stimulation). People who take medicine to control high blood pressure must be careful to follow the doctor’s directions and take the medications as prescribed. Medicines that lower cholesterol and triglycerides may provide protection against the harmful effects of these health problems. The reduction of symptoms for the metabolic club may also reduce harmful immune responses in the body triggered by these health problems.

Recommendations For Middle-Aged Persons About Avoiding The Metabolic Syndrome
Exercise, proper diet, vitamin supplementation, and sensible weight are key parts of successful aging and maintaining your intellect for as long as possible. These efforts are simple and cheap. The benefits can be dramatic to individuals.
1. Exercise at least four times per week.
2. Check your blood pressure every three to six months.
3. Watch your weight.
4. Ask your doctor about your blood sugar, cholesterol, and triglycerides.
5. Eat a proper, balanced diet.

CLICK HERE FOR MORE INFORMATION – 2513.96
A Consumer’s Guide to Understanding the Metabolic Syndrome or How to Quit Club Metabolique

What is the metabolic syndrome?
The metabolic syndrome has many names, including dysmetabolic syndrome, syndrome X, insulin resistance syndrome, and several others. The term, “metabolic syndrome” is applied to persons who suffer from obesity around the waist line, elevated cholesterol or triglycerides, and high blood pressure. These individuals usually suffer from Type II diabetes, which is common in older persons.

Why is the metabolic syndrome important?
The metabolic syndrome is important for three reasons: 1) people with the metabolic syndrome may have increased risks for heart attacks, stroke, and intellectual decline with aging, 2) the metabolic syndrome is often preventable, and 3) the metabolic syndrome can be treated in all persons and eliminated in many people.

What are the consequences of having metabolic syndrome?
People with chronic metabolic syndrome have increased risks of heart attack, stroke, and intellectual loss overtime. The heart attack and stroke may be a direct consequence of high blood pressure and elevated lipids. The intellectual loss may result from blood vessel damage in the brain, poor pump function of the heart, or other consequences of the syndrome. People with metabolic syndrome may have high, increased levels of insulin because their body does not respond to this hormone properly. These high levels of insulin can be harmful to the brain. People with metabolic syndrome may also suffer from increased inflammation directed against the body’s organs, including the brain. The cause of the enhanced inflammation is unknown, but this response may worsen brain damage produced by Alzheimer’s disease or other brain injury.

What can I do to reduce the risk to my health and intellect produced by metabolic syndrome?
Exercise, weight control, and good primary health care are highly effective in reducing the risk for metabolic syndrome. Middle-aged persons should monitor their health status and reduce health risks.

Why is that spare tire so dangerous to my health?
Beltline obesity is frequently referred to as your “spare tire”. This mass of fatty tissue is mostly located inside the abdominal cavity in a shroud of fatty tissue that hangs like an apron from your rib cage. This sheet of tissue expands as a person becomes obese and contains cells that produce a wide range of hormones. This fatty tissue is extremely active in altering levels of blood sugar, fats, and other molecules involved with energy and obesity. Obesity changes many body functions that can damage blood vessels and the brain. Exercise and calorie restriction are the best ways to deflate that spare tire and protect your brain.

What can I do to prevent the metabolic syndrome?
There are many steps a person can take in middle life that may reduce the risk for metabolic syndrome in later life: 1) control your weight and deflate your spare tire, 2) check your blood pressure on a regular basis and take medications prescribed by your doctor to manage your blood pressure, 3) have your doctor check your cholesterol and triglycerides on a regular basis, 4) eat a sensible diet that is low in red meat and include two portions of fish per week, 5) if you have high cholesterol, take your medicine as prescribed by your doctor, and 6) exercise on a regular basis.
10. Medication Management
10. Managing Medication Management

Patient non-compliance is the major obstacle to a dementia prevention program in the primary care setting. Polypharmacy, adverse drug reactions, and patient non-compliance are common problems in patients over the age of 65 that contribute to many hospital admissions. Studies show that between 10-20% of medications consumed by elders are used in error, producing 10% of hospitalizations. Duplicate therapy, incorrect prescriptions, inaccurate dosing, and drug-drug interactions are common problems. Psychotropic medications are often mis-prescribed, especially benzodiazepines or narcotics such as Darvon. Many older persons intentionally use excessive medications or those prescribed for others; especially psychotropic or analgesic drugs. The adverse health effects of inappropriate medications are significant. Inappropriate consumption of psychotropic medications can produce delirium that results in disability or nursing home admission.

Therapeutic non-compliance produces serious medical complications in elders. Depressed elders, elders treated by multiple doctors or those who use multiple medications have greater risk for non-compliance. Elders with unrecognized dementia may forget symptoms, instructions, or dosage changes. Elders may fail to comply with diet, medication, and lifestyle changes for many reasons. About 1/3 of elders admit to medication non-compliance and 3/4 are non-compliant during direct monitoring. Many elders fail to use written instructions for medications and rely on their memory for compliance. Physicians must communicate directly with the older patient to enhance their sense of self-determination and responsibility for their health (Click here for references – 2514.13).

Recommendation

Elders should be encouraged to bring all consumed medications to every office visit and seek consultations from their local pharmacist. Discuss compliance and prevention in explicit concrete terms with the older patient. Provide written instructions and frequent reminders about medication. Include family caregiver in the discussion about medication. Advise elders to cross-check all medications with their pharmacist, including over-the-counter medications. For more information, click here – 2514.11, 2514.15.
A Primary Care Guide To The Role Of Patient Compliance And Prescriptive Safety In Maintaining Cognitive Function

1. Overview
The successful management of chronic diseases usually requires a combination of pharmacological and health behavior interventions. A successful program requires accurate prescription by the physician and compliance by the patient. Prescriptive safety and compliance are essential in the prevention or treatment of dementia or management of diseases that worsens cognitive function. Medication non-compliance may account for up to one-third of hospital admissions among the elderly. Adverse drug reactions produced by appropriately consumed medications account for about 10% of hospitalizations. Even in monitored clinical trials, medication adherence ranges from 43% to 78% (19). Dispensing errors occur in community, pharmacies, and healthcare institutions (See Table 1).

The DETA Dementia Prevention Program focuses on health conditions with defined effective treatments that may reduce risk factors for dementia. For example, the long-term health problems produced by metabolic syndrome may be reduced by managing each of the disorders’ component including hypertension, dyslipidemia, diabetes and obesity. Reduction of severity of metabolic syndrome may reduce the risk for cognitive loss. CLICK HERE FOR MORE INFORMATION – 2513.91. The success of any dementia prevention program will depend on long-term medication and health behavior adherence by the patients.

2. Compliance with Pharmacological Interventions for Chronic Health Problems in Adults
Medication compliance is affected by a complex mixture of clinical factors including the patient’s functional ability, as well as prescribing and dispensing details. Studies demonstrate that depressed individuals and those with impaired cognitive function, as well as those with low health literacy, are more likely to struggle with following complex pharmacological instructions. For instance, cardiac patients with depression have a threefold increased risk for medication non-adherence (13), (21), (22). Physicians that utilize polypharmacy without adequate patient education increase the likelihood of non-adherence by patients. Pharmacies can assist with problems through patient/customer education. The net cost to the healthcare system for medication non-compliance for older individuals is estimated at one-hundred billion dollars per year. A recent review of non-compliance among community residing elders receiving an average of nine medications indicated that in a sample of 100 individuals, only 35% had adequate health literacy to master medication compliance (20). Follow-up studies have demonstrated that 53% of individuals were non-adherent and about one-third of patients were administered medications which were ineffective or contraindicated for older patients (1). Low health literacy increases health expenditures by Medicare recipients (34). For instance, cardiac patients with depression have a threefold increased risk for medication non-adherence (13), (21), (22). Compliance with medical therapy for disorders such as hypertension, diabetes, and hyperlipidemia may reduce the risk for cognitive loss in later life; however, studies show that adherence ranges from one-third to two-thirds among patients with each disease. Patient non-compliance complicates effective medical management of many common disorders including hypertension, diabetes, dyslipidemia, osteoporosis, and glaucoma (See Table 2). As an example, hypertension is a significant risk factor for cognitive loss in later life. Compliance studies that span 10 years in large populations indicate that only 39% of hypertensive patients engage in continuous use, while 22% will start and stop medications and 39% are simply non-compliant with medications. A review of 33 compliance studies showed that about 49% of interventions improved adherence and about one-third produced symptom improvement (23).

---

Table 1. Medication Dispensing Errors by Location

<table>
<thead>
<tr>
<th>Location</th>
<th>n</th>
<th>Outcome</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitals/SNF</td>
<td>56 institutions</td>
<td>19% doses in error and 7% potentially harmful</td>
<td>2</td>
</tr>
<tr>
<td>Community Pharmacies</td>
<td>50 pharmacies</td>
<td>1.7% error rate (6.5% clinically important)</td>
<td>3</td>
</tr>
</tbody>
</table>

2013.14 Medication Management

---
Table 2. A sample of medication compliance studies for common chronic diseases in older persons

<table>
<thead>
<tr>
<th>Disease</th>
<th>n</th>
<th>t</th>
<th>Outcome for Medication Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBP (USA)</td>
<td>2,325</td>
<td>10 yrs.</td>
<td>39% full compliance, 22% partial compliance, 39% full non-compliant</td>
</tr>
<tr>
<td>HBP (Italy)</td>
<td>13,303</td>
<td>1 yr.</td>
<td>42% discontinue, 🔺 medical expenses</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6,090</td>
<td>1yr.</td>
<td>46% non-adherent</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>4,776</td>
<td>3 yrs.</td>
<td>42 to 47% non-adherence</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>38,120</td>
<td>1.7 yrs.</td>
<td>34% non-compliant</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>5,300</td>
<td>6 mos.</td>
<td>1/2 non-compliant</td>
</tr>
</tbody>
</table>

n=number of study subjects  t=duration of study

3. Assessing Medication Compliance
Specific, clinical conditions increase the likelihood of non-compliance, including depression, cognitive impairment, polypharmacy and poly-physicians, i.e., use of multiple doctors (24) (See Table 2). The shopping bag sign, i.e., a shopping bag full of medications, can be disquieting to a physician; however, the provision of a comprehensive list of medications is greatly appreciated by most doctors. Patients may consume four broad classes of medications: 1) prescription drugs, 2) over-the-counter preparations, 3) medications prescribed for other individuals such as a spouse, and 4) medications that don’t seem like drugs, such as alcohol, nicotine, and caffeine. Physicians often focus on prescribed and over-the-counter preparations; however, groups 3 and 4 are important. For example, individuals may use sleeping or pain pills prescribed for a spouse because “they seem to work pretty well for the other individual”. The consumption of alcohol can produce drug-drug interactions and cigarette smoking can induce hepatic enzymes within the cytochrome P450 system. Individuals who cease drinking or smoking may produce alterations of medications that were previously stable and effective at the present dose.

4. Understanding The Effect Of Adverse Drug Reactions On Healthcare And Cognitive Function
The risk for adverse drug reactions is displayed in Table 3 based on the location of the individual. Hospitalization of elders may involve adverse drug reactions in up to one-fourth of individuals with 16.8% developing an adverse drug reaction and 11.4% demonstrating non-compliance causing hospitalization (25), (26). The Beers Criteria for appropriate versus inappropriate drugs were created in response to the frequency of elderly individuals receiving inappropriate medications, especially psychoactive drugs (1). Data based on the Beers reviews indicates that psychotropic medications are often mis-prescribed for older individuals producing avoidable hospitalization or death (23), (27), (28). (See Table 4). Persons with dementia are quite susceptible to complications of commonly prescribed medications and multiple medications may accelerate functional deterioration (36). Psychotropic medications top the list of harmful drugs in the elderly (1). Polypharmacy predicts poor health outcome (37).

Table 3. Adverse Drug Reaction Rates In Older Persons in Hospitals and Nursing Homes

<table>
<thead>
<tr>
<th>Location</th>
<th>n</th>
<th>t</th>
<th>Results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nursing Home (n=2)</td>
<td>332</td>
<td>4 yrs.</td>
<td>67% at least one ADR, cardiovascular most common</td>
<td>4</td>
</tr>
<tr>
<td>Nursing Home (n=10)</td>
<td>28,839</td>
<td>1yr.</td>
<td>1.89 per 100 resident-months, 6% life-threatening, 38% serious</td>
<td>5</td>
</tr>
<tr>
<td>Hospital meta-analysis</td>
<td>39 studies</td>
<td>META</td>
<td>2.1% serious ADR and 0.19% fatal</td>
<td>6</td>
</tr>
<tr>
<td>Community to hospital (n=111)</td>
<td>28,411</td>
<td>10 yrs.</td>
<td>3.4% all admit caused by ADR</td>
<td>7</td>
</tr>
</tbody>
</table>

*Patients received medications in community and required hospital admission
n=number of study subjects  t=study duration  CS=cross-sectional
5. Compliance with Health Behaviors

Cognitive wellness interventions for middle-aged and older individuals involve long-term personal commitment to healthy life choices including exercise, intellectual stimulation, sobriety, weight control, and adherence to medications which are commonly under-utilized by patients. Insufficient data is available to determine the best possible means to maximize appropriate health behaviors that reduce conditions, such as metabolic syndrome. Patient education about the beneficial effects of medication compliance and behavioral adherence would seem a reasonable prudent step in promoting management strategies that might maximize cognitive function in later life (29), (30), (31), (38).

Office schedules and financial pressures will often limit the time available to the primary care physician or pharmacist; however, non-compliance or adverse drug reactions will significantly reduce the benefit of the visit.

Medication compliance is a problem in both standard healthcare paradigm and in the managed care system. For example, non-adherence for anti-diabetic medication in a managed care setting significantly increases associated healthcare expenses such as emergency room visits, etc. (32).

6. Recommendation

Primary care physicians orchestrate the proper pharmacological management of older persons. In a recent caregiver survey, 51% of respondents reported that their physicians do not speak to each other (33). Treatment compliance can improve cognitive function by: 1) avoiding adverse drug reactions, 2) encouraging adherence with medications for chronic diseases that increase risk for dementia, and 3) promotion of lifestyle changes that promote cognitive function. Available studies do not define a “gold standard” method to maximize compliance. Several steps may improve adherence to medication programs:

1. Ask the patient to bring all pill bottles to visit, including OTC’s.
2. Check for depression or mild dementia as risk factors for non-compliance.
3. Discuss benefit and side effects for each drug.
4. Encourage the patient to discuss their medications with pharmacists or home health nurses.
5. Insist on the use of a pill box or medication calendar to facilitate compliance.
6. Simplify dosing schedules as much as possible.
7. Identify and praise good compliance.
8. Check blood levels, when possible, if the patient is non-responsive to appropriate dosing.
9. When appropriate, include spouses or caregivers in discussions about medication compliance and health behaviors.
References


33. Powers RE, et al. (unpublished data)


Physician Fact Sheet
For Statin Therapy As A Protection Against Cognitive Loss In Elders

1. Elevated triglycerides and low HDL cholesterol levels are components of the metabolic syndrome.

2. Most statins reduce LDL-C by at least 30 to 35%.

3. Statin therapy significantly lowers coronary events by as much as 20% to 40%, but long-term medication compliance is low (about 50%).

4. Cardiovascular health is integral component to cerebrovascular fitness.

5. Statins may directly alter the metabolism of A-beta 42 amyloid protein.

6. Some studies suggest that chronic statin therapy may reduce the risk for cognitive decline.

7. Some studies suggest that statin therapy may alter the natural history of persons with mild to moderate Alzheimer’s disease.

8. Statin therapy can be a component of dementia prevention in persons with dyslipidemias.

9. Insufficient data exists to warrant the prophylactic use of statins in the prevention of dementia or the treatment of Alzheimer’s disease.

10. The potential cognitive protection of statin therapy can be used to encourage compliance in middle-aged and older patients.
A Consumer’s Guide To Understanding Medications That Control Cholesterol And Triglycerides

The Role Of Cholesterol And Triglycerides In The Human Body
Cholesterol and triglycerides are molecules in the human body that play essential roles in energy as well as cell structure and these substances are often called lipids. People with excessive amounts of cholesterol and triglycerides have increased risks for certain health problems. Excessive amounts of these fatty substances can increase the risk for heart disease, stroke, and damage to blood vessels. Scientists have not proven a relationship between the risk for dementia and the severity of abnormalities for cholesterol and triglycerides. Scientists have shown that persons who take lipid lowering medications will reduce their risk for developing dementia in later life.

Treating Abnormal Lipids
People can lower cholesterol and triglycerides through diet, weight control, exercise, and medications. Heart-healthy diets that replace red meat with fish are good life choices.

Several forms of cholesterol are present in the body including low density (LDL) or bad cholesterol and high density (HDL) or good cholesterol. People need the proper ratio of the low and high density molecules or they may have increased risk for heart or blood vessel disease. Doctors focus on enhancing good cholesterol while reducing bad cholesterol to the minimum amount. Cholesterol medication will lower bad values or enhance good cholesterol. All such agents seem to have a beneficial effect for reducing the risk of dementia.

Protecting the Brain by Treating Lipids
People with elevated cholesterol and triglycerides can help their brain by protecting blood vessels and heart that sustain brain function. Persons with abnormal cholesterol and triglycerides can help protect their brain against dementia by controlling weight, exercising properly, and taking medications to reduce the level of bad cholesterol, increase good cholesterol, and reduce triglycerides.

Scientists have not performed research to confirm the precise value of managing cholesterol and triglycerides as a method of protecting your brain against Alzheimer’s disease. This research may never be performed; however, available information suggests the protective value of treating disorders of cholesterol and triglycerides. Common sense tells people that these steps will benefit some persons’ long-term mental function.

We recommend that you take every possible step to control cholesterol and triglycerides in order to reduce your risk for dementia.

Recommended Steps:
1. Control your weight.
2. Eat a healthy, balanced, heart-healthy diet.
3. Ask your doctor about your cholesterol and triglyceride levels.
4. Take medications prescribed to control your cholesterol and triglycerides.
11. STATINS
1. Overview:

The primary care physician may be queried about the role of dyslipidemia and statin therapy in the pathogenesis or prevention of dementia. Elevated cholesterol and triglyceride levels are significant health problems in middle-aged and older individuals. Reduction of low density lipoprotein cholesterol by 25% to 40% will diminish the frequency of coronary events by 20 to 40%. Longitudinal studies demonstrate as much as 24% reductions in cardiovascular events after long-term treatment over 5 to 6 years. Elevated cholesterol and triglyceride levels are integral parts of the metabolic syndrome which afflicts approximately 25% of older Americans (5).

2. Mechanisms of Action

The potential protective mechanisms of statin use for cognition include: 1) reduction of damage to large caliber and small caliber vasculature, 2) reduction of inflammation in the brain, and 3) retardation of amyloid deposits. Despite these proposed mechanisms, the overall data on protective effect of statin usage remains unclear (11). A review of nine recent studies on the impact of statin therapy in cognition and dementia provided mixed results (11). A meta-analysis of 7 studies with 13,920 subjects demonstrated reduction of dementia (~30%) and Alzheimer’s disease (~20%) with treatment; however, this effect “signal” was lost in the study’s “noise”. A variety of studies using multiple research techniques including longitudinal studies, nested case matching, and other statistical methods provide conflicting data. The CSF beta amyloid levels in older individuals do not appear affected by statin usage; however, plasma beta amyloid 42 levels in non-demented persons over age 75 appear slightly diminished in subjects receiving long-term statin therapy (12). The clinical significance of these scientific observations remains unclear. Treatment with Atorvastin may enhance cognitive function in persons with mild or moderate dementia (17).

Cell culture and rodent studies indicate that statin therapy may reduce the deposition of amyloid or impede aggregation of amyloid fibrils. No benefit is presently identified against the hyper-phosphorylation of tau or other markers for the production of neurofibrillary tangles. Neuropathological studies in humans who receive statin therapy prior to death indicate a strong linear association between increased LDL cholesterol levels and increased numbers of senile plaque or neurofibrillary tangles (13).

3. Clinical Recommendations

The global vascular benefit of statin therapy is supported by most research. Treatment of individuals with abnormal lipid levels is recommended, regardless of the patient’s age. The prophylactic use of statins to prevent dementia in persons with normal lipids is not recommended because the risk-benefit ratio does not support the use of these expensive agents (15). The treatment of dyslipidemia in the setting of metabolic syndrome may provide greater benefit, as this intervention may assist with the reduction of intrinsic, brain inflammatory responses. No specific type of medication or diet has been demonstrated as potentially more beneficial for possible cognitive protection. The beneficial effect of statin therapy in mild to moderate dementia also remains controversial (11), (14), (15).

Statin therapy may produce numerous risks and side effects including myalgias and hepatotoxicity with some agents (16). Long-term compliance with diet and medication is a therapeutic challenge in the primary care setting. Longitudinal studies suggest that about 50% of patients comply with long-term statin therapy. Sufficient data exists about brain protection to provide the additional encouragement that long-term lipid management may significantly reduce the risk for cerebrovascular events and cognitive decline in later life. Strict adherence to lipid management may provide a significant beneficial, cognitive effect to those individuals with dyslipidemias (18) *(For more information on compliance, See 2514.1)*. Dietary restriction of trans-fat may further reduce the risk for dementia.

**Recommendations**

1. Check lipid profiles in older persons.
2. Promote diet and weight control as lipid lowering interventions.
3. Treat dyslipidemia when identified in patients.
4. Use the concept of brain protection to encourage compliance with statin medications.
5. Do not use statins as a “preventive” measure against dementia in persons with normal lipid profiles.
6. Use “brain protection” as another argument to promote medication and dietary compliance in patients with hyperlipidemia.
References:


1. Elevated triglycerides and low HDL cholesterol levels are components of the metabolic syndrome.

2. Most statins reduce LDL-C by at least 30 to 35%.

3. Statin therapy significantly lowers coronary events by as much as 20% to 40%, but long-term medication compliance is low (about 50%).

4. Cardiovascular health is integral component to cerebrovascular fitness.

5. Statins may directly alter the metabolism of A-beta 42 amyloid protein.

6. Some studies suggest that chronic statin therapy may reduce the risk for cognitive decline.

7. Some studies suggest that statin therapy may alter the natural history of persons with mild to moderate Alzheimer’s disease.

8. Statin therapy can be a component of dementia prevention in persons with dyslipidemias.

9. Insufficient data exists to warrant the prophylactic use of statins in the prevention of dementia or the treatment of Alzheimer’s disease.

10. The potential cognitive protection of statin therapy can be used to encourage compliance in middle-aged and older patients.
Physician Fact Sheet On The Role Of Statins And Dementia

1. Hyperlipidemia plays a role in cardiovascular disease and cerebrovascular disease.

2. Hyperlipidemia is a component to the metabolic syndrome.

3. The data on the relationship between lipid level and the risk for dementia is unclear.

4. Statin medications are highly effective at normalizing lipids.

5. Dietary and weight control continue to be a mainstay for lipid management.

6. Animal models suggest statins may alter the inflammatory response to amyloid or retard amyloid deposition in the brain.

7. The “brain-protecting” effect of chronic statin therapy is controversial because many studies support the effect and others fail to document a CNS benefit.

8. Prophylactic statin therapy in people with normal lipids is not recommended to prevent dementia.

9. Aggressive management of lipids in older persons may have a secondary benefit of protecting the brain.

10. Physicians can use the potential “brain-protective” impact of statins to promote compliance which is about 40% in the general public.
The Consumer’s Guide to Understanding the Role of Elevated Cholesterol or Triglycerides in Dementia

How does lowering bad cholesterol and triglycerides protect me against developing dementia?
Abnormal levels of cholesterol and triglycerides are common health problems in the older population. Long-term abnormal levels of these two substances called “lipids” are associated with increased risk for heart and blood vessel disease. Most lipid lowering medications are called “statins”, and these drugs may reduce your risk of developing dementia in later life. Regular exercise, weight control, and a healthy diet may reduce lipid levels of at all ages.

Medications that reduce cholesterol or triglycerides may help to protect intellectual function by several ways. First, the large and small vessels in the brain may be damaged by fatty deposits in arteries resulting from long-term elevation of lipids. Lowering the levels of bad cholesterol and triglycerides may lower the risk of heart and blood vessel damage. Second, lipids may play a role in the accumulation of toxic proteins in the brain called “amyloid” and the anti-lipid medication may reduce these toxic deposits.

The best available science shows that high levels of bad cholesterol and triglycerides are bad for your brain. Persons with unhealthy lipids should exercise, eat a healthy diet, and take medications to lower the lipids. There is strong evidence that lowering your lipids will reduce damage to the heart and blood vessels that injures the brain. People with normal triglycerides and normal cholesterol should not take statin medications to protect against dementia because the risk of these medications is not worth an unproven benefit in persons with normal lipids.

Suggestions:
1. Eat healthy.
2. Exercise and control your weight.
3. Talk to your doctor about cholesterol and triglycerides.
4. Take your statins when you have unhealthy lipids.
A Consumer’s Guide to Understanding Medications That Control Cholesterol and Triglycerides

The Role Of Cholesterol And Triglycerides In The Human Body
Cholesterol and triglycerides are molecules in the human body that play essential roles in energy as well as cell structure and these substances are often called lipids. People with excessive amounts of cholesterol and triglycerides have increased risks for certain health problems. Excessive amounts of these fatty substances can increase the risk for heart disease, stroke, and damage to blood vessels. Scientists have not proven a relationship between the risk for dementia and the severity of abnormalities for cholesterol and triglycerides. Scientists have shown that persons who take lipid lowering medications will reduce their risk for developing dementia in later life.

Treating Abnormal Lipids
People can lower cholesterol and triglycerides through diet, weight control, exercise, and medications. Heart-healthy diets that replace red meat with fish are good life choices.

Several forms of cholesterol are present in the body including low density (LDL) or bad cholesterol and high density (HDL) or good cholesterol. People need the proper ratio of the low and high density molecules or they may have increased risk for heart or blood vessel disease. Doctors focus on enhancing good cholesterol while reducing bad cholesterol to the minimum amount. Cholesterol medication will lower bad values or enhance good cholesterol. All such agents seem to have a beneficial effect for reducing the risk of dementia.

Protecting the Brain by Treating Lipids
People with elevated cholesterol and triglycerides can help their brain by protecting blood vessels and heart that sustain brain function. Persons with abnormal cholesterol and triglycerides can help protect their brain against dementia by controlling weight, exercising properly, and taking medications to reduce the level of bad cholesterol, increase good cholesterol, and reduce triglycerides.

Scientists have not performed research to confirm the precise value of managing cholesterol and triglycerides as a method of protecting your brain against Alzheimer’s disease. This research may never be performed; however, available information suggests the protective value of treating disorders of cholesterol and triglycerides. Common sense tells people that these steps will benefit some persons’ long-term mental function.

We recommend that you take every possible step to control cholesterol and triglycerides in order to reduce your risk for dementia.

Recommended Steps:
5. Control your weight.
6. Eat a healthy, balanced, heart-healthy diet.
7. Ask your doctor about your cholesterol and triglyceride levels.
8. Take medications prescribed to control your cholesterol and triglycerides.
12. DIABETES
The Primary Care Guide To Understanding The Role Of Diabetes As A Risk Factor For Cognitive Loss Or Dementia In Adults

1. Introduction
Glucose intolerance is common in older individuals and this metabolic symptom can progress to Type II diabetes in older individuals. Type II diabetes is an integral part of the metabolic syndrome in midlife that increases the risk of cognitive loss in later life. Glucose intolerance and diabetes in midlife produce a two-fold increased risk of cognitive loss in later life (8). Older diabetic individuals are more likely to have hypertension, cardiovascular disease, and atherosclerosis that produce diseases associated with dementia, including heart disease and renal failure.

Primary care physicians can encourage middle aged individuals to comply with weight loss, exercise, and dietary discretion by discussing the potential benefit for late life cognitive function, especially those individuals with strong family histories for Alzheimer’s disease (8), (9).

2. The Molecular Function Of Insulin In The Brain
Studies show substantial numbers of insulin receptors in the cerebral cortex and hippocampus of the human brain (10). Insulin receptors are linked to second messenger systems within neurons that may control the production of neurofibrillary tangles through the regulation of phosphorylation of the microtubule-associated protein “tau”.

Insulin serves many functions in the human brain, including: 1) the regulation of glucose metabolism, 2) mediation of a neurotrophic effect, 3) signal transduction, and 4) modulation of neuroendocrine function. The role of insulin far exceeds simple regulation of glucose that is available to the cerebral cortex via the blood supply.

Brain insulin receptors are diminished in the cerebral cortex during normal aging; however, their density appears greater in persons with Alzheimer’s disease versus aged-matched controls. This finding may suggest a compensatory upregulation of insulin receptors to compensate for insulin resistance (19).

The activity of insulin degrading enzyme (IDE) is diminished in brain tissue from Alzheimer’s patients as compared to controls. This enzyme also metabolizes intracellular and extracellular Aβ amyloid. Individuals with APOE 4 genes have diminished mRNA expression for IDE in the human hippocampus. Rodent models for Alzheimer’s disease demonstrate that elimination of the IDE gene through knockout models increases relative concentration of Aβ in the brain. Hyperinsulinemia can provoke increased markers for inflammation and beta amyloid protein in older humans (18).

3. Clinical studies of diabetes and dementia
Multiple studies have examined the relationship between glucose intolerance or diabetes and cognitive loss or Alzheimer’s disease. The majority of studies demonstrate a modest relationship of impaired glucose tolerance to either diminished cognitive function or risk for
Alzheimer’s disease. Although a few studies have questioned this result, the majority support the observation that diabetes is a risk factor developing dementia in later life (See Table 1).

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Duration</th>
<th>Outcome</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1811</td>
<td>30 yrs</td>
<td>History and duration ↑ risk</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>915</td>
<td>CS</td>
<td>Only minor ↑ cognitive function</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>999</td>
<td>4 yrs</td>
<td>Cognitive function in white women</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>10963</td>
<td>6 yrs</td>
<td>Cognitive function</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>6330</td>
<td>CS</td>
<td>↑ relationship (1.3 / 1.0 to 1.9)</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>5647</td>
<td>15 yrs</td>
<td>Associated with selective poor</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>1455</td>
<td>15 yrs</td>
<td>Risk for dementia</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>5510</td>
<td>CS</td>
<td>↑ Insulin = ↓ cognitive function</td>
<td>11</td>
</tr>
</tbody>
</table>

A comparison of cerebral spinal fluid findings from individuals with Alzheimer’s disease versus age-matched controlled individuals demonstrates that Alzheimer’s patients have diminished CSF insulin in contrast to increased serum insulin, suggesting increased insulin resistance in the brain.

Overall, cross-sectional and longitudinal studies suggest a relative, two-fold increased risk for developing cognitive loss in persons with glucose intolerance or diabetes. Individuals with metabolic syndrome, or diminished physical activity in midlife experience increased risk for developing dementia in later life (8). CLICK HERE FOR MORE INFORMATION ON THE METABOLIC SYNDROME 2513.91.

4. Brain Pathology in Persons with Diabetes
The brains of elders with diabetes demonstrate a range of pathological findings to include increased risks for cerebral infarcts and small vessel disease, especially in those individuals with hypertension. Postmortem brain specimens form aging individuals with diabetes do not have greater densities of senile plaques than non-diabetic elders but they demonstrate increased rates of micro and macro infarcts. Demented individuals with both diabetes and APOE 4 genotype have the highest densities of neurofibrillary tangles and senile plaques at autopsy (12), (13). Elevated glycated hemoglobin A1 (HbA1c) may be correlated to accelerated atrophy in elders as demonstrated by brain imaging (17).

5. Conclusion About the Relationship of Cognition and Diabetes
Systemic insulin dysregulation may accelerate damage in the aging human brain through several mechanism, including: 1) increased glucose utilization, 2) increased oxidative stress, 3) accelerated tau phosphorylation, and 4) reduced insulin degrading enzyme that increases amyloid load in the brain (20). Randomized controlled studies to examine the relative benefit of glucose control versus untreated diabetes will not be performed for obvious ethical and legal reasons. The best available information suggests that reduction of health risk
factors for glucose intolerance in midlife through weight control, exercise, and dietary discretion may reduce the risk for late life diabetes. Aggressive management of hyperglycemia in later life may further reduce risk factors for dementia associated with glucose intolerance. Severe episodes of hypoglycemia also correlate to diminished cognitive function (14), (15). Careful management of blood sugars may slightly improve cognition in some elders. (16).

Primary care physicians are justified in advising middle-aged individuals and older patients that risk reduction for diabetes is one of many steps that may reduce risk of late life cognitive loss. Compliance data suggest that about half of diabetic patients are compliant with hypoglycemic agents and the promise of the brain benefit can be added to other potential protections for organs such as heart, eye, kidney, and others. This advice may particularly impact individuals with family histories for Alzheimer’s disease or other types of dementia. FOR MORE INFORMATION, CLICK HERE 2514.11.

Recommendations to Primary Care Physician

1. Weight control and regular exercise may reduce the risk for diabetes and dementia.
2. Inform patients that risk reduction of glucose intolerance is a component of dementia prevention.
3. Meticulous control of blood sugars in diabetic patients may enhance cognition.
4. Severe or sustained hypoglycemia may be a risk factor for dementia.
REFERENCES:

Physician Fact Sheet On The Relationship Between Diabetes And Dementia

1. Persons with diabetes in midlife have about a two-fold increased risk for cognitive loss in later life.

2. Risk factors for diabetes such as midlife obesity and physical inactivity are also risk factors for Alzheimer’s disease or vascular dementia in later life.

3. The human brain has substantial numbers of insulin receptors in the neocortex and hippocampus.

4. Insulin degrading enzyme activity may also affect the amount of cerebral amyloid.

5. A combination of diabetes and APOE 4 typing increases the risk for senile plaques and neurofibrillary tangles at time of death.

6. Long-term patient compliance for oral hypoglycemic medications is about 50%.

7. Diabetes is a risk factor for other health problems that increase the risk for dementia, including cardiac dysfunction and renal failure.

8. Randomized controlled studies will not be done to confirm the preventive benefit for cognition of lifetime glucose management.

9. Physicians can advise individuals at risk for dementia that weight control and proper diet may reduce the risk for later life intellectual loss.

10. Aggressive management of blood sugars in later life may provide a small enhancement for cognitive function.
A Consumer’s Guide To Understanding The Role Of Diabetes And Dementia

Diabetes is a disease, which is diagnosed by blood tests for high blood sugars. Glucose is a sugar, which is the source of energy in our brain, and the body regulates glucose by production of the hormone, insulin. Insulin acts through a communication system which includes special areas on the outside of cells that collect the insulin and command the cell to use the sugar. These specialized zones are called “receptors” and stimulation of the insulin receptor can produce many changes in the cell. Different types of tissue use insulin in different ways, including the brain.

High blood sugars occur when the body does not produce or use enough insulin. Most children with diabetes do not make enough insulin. The adult body may not respond to normal amounts of insulin, such as in older diabetics with obesity. The failure to respond to insulin is referred to as “insulin resistance” and this condition is common in many older persons, especially those with obesity and lack of exercise.

Insulin is important to the brain because the brain uses a lot of energy. Too much insulin in the blood stream can be harmful to the brain. This form of insulin toxicity may contribute to some of the intellectual loss that is seen in persons with diabetes.

Untreated or under-treated diabetes is bad for blood vessels. People with chronic diabetes can develop more hardening of the arteries and increased risks for heart damage.

Middle-aged people with diabetes can help to protect their brain by controlling their weight and using their medication to control their blood sugar. Poor control of diabetes may increase damage to heart blood vessels in brain. The fatty tissue that accumulates with obesity reduces the efficiency of insulin in your body. Regular exercise and weight control may help reduce the impact of diabetes in the brain.

Scientists have not performed the research to confirm the benefit of exercise, weight control, and strict control of blood sugar on the long-term risk of developing dementia for persons with diabetes. Common sense suggests that these actions will reduce risks associated with this common disease.
A Consumer Guide To
Understanding The Role Of
Diabetes In Dementia

What is diabetes?
Diabetes is diagnosed when a person has high blood sugars. Diabetes is divided into Type I, which often occurs in younger persons and Type II, which is common in older persons. Many persons with Type I diabetes need insulin while persons with Type II can use medicines that increase the body’s ability to produce and release insulin. Chronic high blood sugars are bad for your brain and bad for your body. Many years of elevated blood sugar may increase the risk of heart disease and blood vessel damage. Persons with chronic, poorly controlled diabetes may develop kidney disease, nerve disease, and blindness after 20 or 30 years. Diabetes will double your risk for developing dementia in later life.

What causes diabetes?
Your risk for developing diabetes is a mixture of genes, diet, exercise, and weight. Good nutrition along with regular exercise and normal body weight may dramatically reduce your risk of developing diabetes or suffering complications from this disorder.

What can you do about diabetes?
People with diabetes must control their blood sugar to reduce the risk for complications. Proper diet, checking blood sugars, and taking medication are the best ways to control the symptoms of diabetes. People with poor diabetic control have increased risk for developing intellectual loss in later life.

People with a strong family history of dementia should reduce their risk for developing diabetes by controlling weight, diet, and exercise. People who develop diabetes must follow the doctor’s instructions in using medications to reduce risks produced by the disease.

How is diabetes related to dementia?
Chronic diabetes can damage the brain through many pathways including: 1) damage to the heart that sustains the brain, 2) damage to blood vessels in the brain, and 3) production or release of chemicals that can harm the brain. Good control of blood sugar may reduce the risk of damage and protect the brain.
Consumer Fact Sheet on the Role of Diabetes as a Risk Factor for Dementia

1. Persons with diabetes may lose control of their blood sugar, causing high blood sugars.

2. Obesity is a risk factor for diabetes.

3. Physical inactivity is often a risk factor for obesity and diabetes.

4. Diabetes, obesity, and physical inactivity in midlife are possible risk factors for dementia in later life.

5. Diabetes is a serious risk factor for hardening of the arteries, heart malfunction, and other conditions that increase the risk for intellectual loss in older persons.

6. Diabetes is probably a risk factor for dementia caused by hardening of the arteries.

7. Persons with diabetes have increased risks for major strokes and mini strokes.

8. Older persons with high blood sugars have increased risks for memory problems and other forms of intellectual loss.

9. The combination of high blood pressure, high cholesterol, and high blood sugar is very hard on the human brain.

10. Lifestyle changes in midlife, such as diet control, weight reduction, and regular physical exercise will probably help reduce the risk of dementia in later life.
13. GENETICS
Explaining The Role Of Genetics As A Risk Factor For Dementia To Patients In The Primary Care Setting

Overview
Families are often concerned about the possibility that genetics may play some role in the pathogenesis of Alzheimer’s disease (AD). A positive, family history for dementia may increase the patient’s relative risk for developing dementia. Individuals who have a parent or sibling with AD may have 3.5x increased risk of developing the disease; however, the autosomal dominant variant of Alzheimer’s disease is present in only 1-2% of all Alzheimer’s disease cases. Many other forms of dementia, such as vascular and diffuse Lewy body disease have a substantially reduced genetic load in comparison to AD. A variety of genes are associated with familial/early onset AD that include chromosomes 1, 2, 14, and 21, as well as late onset or sporadic disease that includes chromosomes 6, 19, and 21 (1), (2), (3) (See Table 1).

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Disease</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FAD</td>
<td>PSEN 2</td>
</tr>
<tr>
<td>14</td>
<td>FAD</td>
<td>PSEN 1</td>
</tr>
<tr>
<td>17</td>
<td>FTD</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>LOAD</td>
<td>APO E</td>
</tr>
<tr>
<td>21</td>
<td>Down’s LOAD</td>
<td>APP</td>
</tr>
</tbody>
</table>

FAD = familial AD  PSEN = Presenilin  FTD=Frontotemporal Dementia  LOAD = Late onset AD  APP=Amyloid Precursor Protein

Interpretation of the Family History
A family history of Alzheimer’s disease requires a post-mortem confirmation of the reported premortem diagnosis, as studies report a 10% discrepancy between clinical and pathological diagnosis. Many clinical conditions can produce confusion in the older patient and the family history is only as accurate as either the premortem diagnosis or postmortem confirmation.

Assessing the Risk Factors
The relative risk for developing Alzheimer’s disease can be crudely assessed by determining how many family members were affected by the disease and what age these individuals developed symptoms. Individuals who develop dementia early in life, i.e., below age 60, are more likely to have a genetic variant of the disease. Proximity in the family tree may be helpful. An individual with a father and uncle who both develop dementia before age 60 might have a significantly increased risk for developing dementia in comparison to a woman who had a maternal aunt develop the disease after age 80 producing the same risk factors as the general population. A family history of dementia may not confirm the presence of Alzheimer’s disease,
as a post-mortem examination is required to absolutely diagnose the cause of dementia. The presence of one or two alleles will also increase the risk of developing dementia.

**Genetic Testing**

Genetic testing is not presently available for Alzheimer’s disease or any other form of dementia except for Huntington’s chorea. APO lipoprotein E genes are often discussed because the presence of two E4 alleles will increase the risk while homozygote E2 seems protective. APOE typing is now offered as a routine clinical laboratory test. The APOE 4 gene is important but not necessary for dementia (1), (9) and certain ethnic groups, such as pygmies and others, have high rates of APOE 4 without identified increased risk (5), (6), (7), (8). It is unlikely that a single specific gene will be identified for late onset Alzheimer’s disease or most other types of dementia, as the genetic risk may be predicted by a variable mixture of independent and inter-related genetic factors. Assessment of multiple genetics risk factors will probably be required to predict the risk in the future.

**Understanding the Interaction of Genes, Environment, and Health Behaviors**

A variety of health behaviors, e.g., exercise, weight control, or intellectual vitality may interact with medical conditions, e.g., diabetes or hypertension, to amplify the role of genetic predispositions, such as the presence of the APOE 4 allele. This complex equation will require years of further research to clarify and quantitate as a “genetic risk assessment”.

The early onset familial AD accounts for less than 2% of dementia and involves genes that impact the amyloid precursor protein gene. About half of the late-onset cases may be related to the APOE gene which is located on chromosome 19. Unlike the amyloid gene on chromosome 21, the APOE gene is a susceptibility gene that may accelerate the age of onset for symptoms (11). Based on studies in elderly twins, genetic liability in late onset disease accounts for 48% of variation in the risk of developing dementia (3).

International studies comparing African Americans from Indianapolis to genetically similar individuals from their homeland in Nigeria show that APOE typing is less predictive of dementia in native Africans. The reduced risk if dementia in the Nigerian group may result from better health behaviors, such as a better diet and increased exercise.

**Recommendations**

Mixed dementia, such as AD and vascular dementia or AD and diffuse Lewy body disease, has a higher clinico-pathological discrepancy. Individuals, who are concerned about having Alzheimer’s disease in the family, should be encouraged to engage in health practices that protect the brain. Although the value of cognitive fitness programs for persons with strong genetic loads for Alzheimer’s disease is unproven, conventional wisdom suggests that reducing other associated brain injury would prolong the duration of cognitive fitness. Much or most dementia may result from a complex interaction between susceptibility genes, environment and life choices. Future genetic therapy will be complex and require therapeutic techniques not presently available to clinicians (2), (10), (11). CLICK HERE FOR A FAMILY HANDOUT ON GENES AND DEMENTIA.
References

PHYSICIAN FACT SHEET ON THE ROLE OF GENETICS AND DEMENTIA

1. A positive family history for Alzheimer’s disease increases the individual’s risk for developing dementia.

2. A family history of Alzheimer’s disease does not confirm the presence of this disease unless a post-mortem examination is performed.

3. Individuals who have siblings with Alzheimer’s disease have up to a 3.5-fold increased risk for developing dementia.

4. The autosomal dominant variant of Alzheimer’s disease produces about 2% of all dementias.

5. Multiple “suspect” genes are linked with late onset dementia; most associated with the APOE 4 gene on chromosome 19.

6. APOE typing is not predictive for dementia as some ethnic groups have high rates of APOE 4 and normal rates of dementia.

7. In elderly twins, genetic factors accounts for 48% of variation in risk for dementia.

8. Vascular dementia and diffuse Lewy body disease probably have limited genetic risk factors.

9. Frontotemporal dementia is associated with chromosome 17 that programs tau.

10. A simple genetic test is unlikely for Alzheimer’s disease; however, a genetic screen that assesses risk factors is likely within the next five years.

11. Genetic risk can be crudely assessed by determining the number of family members with proven Alzheimer’s disease, age of onset, and proximity in the family tree.

12. Genetic risk factors, basic healthcare compliance, and lifestyle decisions may alter the risk for dementia.
The Consumer’s Guide to Understanding the Role of Genetics in Dementia

Genetics refers to the study of how traits are passed on from parents to children. These traits are the functions that control all aspects of our body and life. Most traits are controlled by genes and environmental factors. Genes are pieces of a complex molecule that code for proteins and other factors that control how cells of your body functions. Each human being has a set of about 30,000 genes located on 46 chromosomes. Changes in these genes can occur due to many factors, for example, radiation, chemicals, and exposure to supercharged forms of oxygen called free radicals.

Errors in the code contained in genes can cause your body to malfunction by producing defective proteins, which can accumulate and reduce proper function in the brain. Some rare genetic causes of dementia, like Huntington’s chorea, cause these defective proteins and these individuals will almost always have this disease. Similar to Huntington’s chorea, a small number of persons with familial Alzheimer’s disease (4% or less) have genes that predestine them to develop dementia. These genes cause intellectual loss early in life, usually before the age of 65.

Some common forms of dementia are more complex and may result from when an accumulation of genetic changes and certain other health problems in middle or later life. Dementia is most likely to occur in later life. Late onset dementia has certain genes that may be only risk factors for developing intellectual loss; however, some people may not get the disease even if they have some of these “risk” genes. Risk factors or risk genes increase the chance that a person will get the disease, but unlike the genes for early onset dementia, having the risk gene does not predestine them to getting the disease. The gene for the protein APOE is considered a risk gene for dementia and the presence of the “high risk” form of APOE (APOE 4) may increase a person’s chance of developing intellectual loss. The “toxic” APOE may increase the rate of intellectual loss by causing symptoms 10 years earlier than others without this high risk gene. Fifty percent or less of those with this high risk marker may develop Alzheimer’s disease.
DO MY GENES DETERMINE MY FATE AS I GROW OLDER?

Your genes determine some aspects of how you grow old and your risk for developing dementia. Genes may play a big role in determining how long and how well you live. Genes also determine your risk for developing health problems that may increase your risk factors for dementia. Heart disease, high blood pressure, and elevated triglycerides or cholesterol can be influenced by your genes. Life choices and healthy behaviors play the biggest role in determining how well you age and how many diseases occur that damage your brain. Genes are important but a healthy lifestyle is equally important. You can’t change your genes, but you can change your lifestyle.

Click here for ways to help your brain age well - 2513.55
THE TEN COMMANDMENTS
FOR Preventing dementia

I. Thou shalt use thy brain for thy whole life. Your brain is a “use it” or “lose it” organ.

II. Thou shalt not become a couch potato. Obesity, inactivity, and poor health are bad for your brain.

III. Thou shalt exercise until the day thy die. People who exercise on a regular basis have better physical and intellectual life.

IV. Thou shalt not keep a spare tire. Obesity around the belt line in middle life is bad for your brain in later life.

V. Thou shalt protect thy heart and blood vessels. Your brain needs adequate oxygen and nutrients to stay well.

VI. Thou shalt treat thy hypertension as a young person to keep thy memories as an old person. Untreated hypertension damages blood vessels in the brain.

VII. Thou shalt take a STANDARD vitamin on a daily basis. B-Complex vitamins and Folic acid are helpful.

VIII. Thou shalt fix thy depression and encourage thy neighbor to fix their depression. Treating depression may improve your physical and intellectual health. Pass the good news to a friend.

IX. Thou shalt avoid gluttony with food and alcohol. Excessive alcohol and elevated cholesterol or triglycerides are bad for the brain.

X. Thou shalt find a good doctor and follow their advice. Smart doctors and wonder drugs are not beneficial when the advice and the medication sit in the medicine cabinet.