Chapter 7

Environmental Factors in the Development of Dementia

Focus on Alzheimer's Disease and Cognitive Decline

In this chapter we will review some of the evidence of the critical role of environmental factors in common forms of dementia, and in cognitive decline more generally. While a comprehensive review of the literature is beyond the scope of this report, we have tried to clarify some of the key drivers. We have limited this review to environmental chemicals, nutrition, health and social conditions, and exercise. We have not considered the potential role of infectious agents, cigarette smoking, caffeine, drugs of abuse, estrogen, and pharmaceuticals, among other factors.

In this chapter we treat several common forms of dementia as a continuum.

As discussed in chapter 5, a growing body of evidence suggests that various forms of neurodegeneration and associated symptoms may be viewed as a continuum. In this chapter we treat several common forms of dementia in particular as a continuum. Likewise, the lack of clear distinction between normal aging, abnormal cognitive decline, and dementia—in both symptoms and histopathology[1]—suggests that the degree of impairment can also be viewed as a spectrum.

In this chapter, we represent this spectrum of common dementias with the compound term "Alzheimer's disease/dementia." This allows us to discuss environmental factors that influence the larger spectrum of inter-related conditions and acknowledges frequently overlapping or mixed pathology. Similarly, we represent the spectrum of clinical severity with the terms "Alzheimer's disease/cognitive decline" or "dementia/cognitive decline." These broadly framed terms are consistent with the emerging view that cognitive decline—and the dementia it may lead to—are products of multiple interacting environmental and genetic influences. The wide variety of these influences is reflected in a continuum of pathologies and symptoms across diagnostic categories and degrees of severity.

The lobster is a symbol for long life and good fortune in Japan, and are especially associated with New Year's festivities and feasts.

We begin by addressing several preliminary subjects that provide a context for discussing environmental influences: the clinical picture of Alzheimer's/dementia, known genetic causes, and gene-environment interactions.

Alzheimer's Disease and Dementia—Clinical Features

Distinguishing normal aging from early dementia in practice is often very difficult.

In the clinical setting, Alzheimer's—like other forms of dementia—is defined as a decline in multiple cognitive functions, including memory, that is severe enough to interfere with daily functioning. The typical early symptoms, as defined by current convention, are difficult to distinguish from "normal" aging: gradual onset of short-term memory problems, language and visual-spatial perception difficulties, and declining executive function, including organizational abilities and efficiency. By definition, however, symptoms that tend to be sporadic, can be compensated for, and are generally non-progressive are considered normal aging. Symptoms that worsen over time and impair basic functions—such as speech fluency and the ability to prepare a meal or pay a bill—are by definition characteristic of dementia. Since the progressive nature of symptoms is key to the diagnosis, the determination that someone has dementia cannot be made at the onset of symptoms. Distinguishing normal aging from early dementia in practice is often very difficult.

The frequency of dementia is strongly related to age, with the prevalence nearly doubling every five years, from about 1.5 percent in 60–69-year-olds to 40 percent in 80–89-year-olds.[2] According to the conventional classification, Alzheimer's is the most common form of dementia, followed by vascular dementia, Lewy body dementia, and frontotemporal dementia.[3] (See chapter 5.)

Genetic Factors in Alzheimer's Disease

Inherited, Early-Onset Alzheimer's

Several genetic mutations increase amyloid-beta production or processing[a] and are associated with early-onset, familial forms of Alzheimer's disease—generally before age 60. Amyloid-beta is the primary constituent of extracellular plaques, typically considered one of the two pathological hallmarks of Alzheimer's disease, whether inherited or sporadic. The extent to which plaques and tangles (the other pathological hallmark), are responsible for neuron degeneration or merely markers of other fundamental processes gone awry continues to be debated, particularly with regard to the more common, late-onset form of the disease.

Amyloid-beta is generated by the cutting of a larger amyloid precursor protein by two enzymes, (beta and gamma secretase), a

[a] *by the gamma-secretase enzyme*

process that occurs in all cells in the body for reasons that are as yet unknown.[4] This process is increased in the aging brain, and much more so in the Alzheimer's brain. Once cut, fragments of amyloid-beta that lie outside the cell may aggregate into small, soluble molecules (oligomers) which can further concentrate into fiber-like structures. Oligomers are toxic to cultured neurons[5] [6] and interfere with learning and memory in studies with laboratory mice. [7]

Down syndrome, a genetic disorder caused by the presence of an extra chromosome (number 21) in the cells of affected individuals, also carries an increased risk for early-onset Alzheimer's disease and dementia.[8] Down syndrome is characterized by intellectual disabilities and various metabolic abnormalities. Postmortem examination of the brains of people with Down syndrome almost universally show amyloid plaques and tau tangles characteristic of Alzheimer's disease, beginning as early as age 8,[9] as well as evidence of excessive oxidative stress and lipid peroxidation.[10] [11] As in the general population, however, some people with Down syndrome with extensive amyloid-beta plaque formation survive into their seventies without evidence of dementia.

Several genes on chromosome 21 are likely to increase Alzheimer's disease risk. Their over-expression in people with Down syndrome, because of an extra copy of the chromosome, may help to shed light on the origins of Alzheimer's disease more generally. The amyloid precursor protein gene is located on chromosome 21 and its over-expression leads to excessive production of that protein. A nearby gene is responsible for producing a protein that influences cholesterol transport within the cell and appears to increase the likelihood that amyloid-beta plaques will form from the excessive levels of amyloid precursor protein.[12] A third nearby gene is responsible for producing the enzyme superoxide dismutase (SOD1). Over-expression of SOD1 contributes to an enzyme imbalance that results in excessive free-radical production, oxidative stress, and damage to critical cellular components.[13] One study concludes that excessive oxidative stress precedes the onset of plaque formation in people with Down syndrome.[14]

Individuals carrying the early-onset Alzheimer's genes have a high incidence of the disease and are affected at a relatively early age. However, these early-onset, genetically determined cases of the disease constitute a very small portion—between 4 and 6 percent—of all Alzheimer's cases.[15]

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Genetics of Sporadic, Late-Onset Alzheimer's Disease—ApoE4

The more common, late-onset, sporadic form of Alzheimer's has no known genetic causes. However, the ApoE4 gene, according to most studies in the developed world,[16] [17] [18] increases the risks of developing Alzheimer's disease/dementia. At least one copy of the ApoE4 gene is typically reported to be present in about 15 percent of the US population[19] and in 5–41 percent of various populations around the world.[20] One meta-analysis found the risk of Alzheimer's disease in Caucasians to be increased approximately threefold in those carrying one copy (also called carriers, or heterozyotes) and nearly 15-fold in those carrying two copies (homozygotes) of the ApoE4 gene.[21] The risks among African Americans varied more between studies, averaging a 1.1 and 5.7-fold increase for African Americans carrying one and two copies of the gene, respectively. ApoE4 is also associated with a number of abnormalities in cognitive function in subjects without Alzheimer's disease.

One meta-analysis found the risk of Alzheimer's disease in Caucasians to be increased approximately threefold in those carrying one copy and nearly 15-fold in those carrying two copies of the ApoE4 gene.

Interestingly, the ApoE4 gene is also commonly (though not uniformly) associated with a variety of other diseases and conditions including vascular dementia, mild cognitive impairment,[22] [23] elevated LDL cholesterol,[24] and cardiovascular disease.[25] [26] [27] One meta-analysis found the cardiovascular risk in ApoE4 carriers increased 1.42-fold.[b] [28]

The ApoE gene plays a key role in lipid transport and processing. The ApoE lipoprotein that the gene produces carries lipid in the blood as well as in the brain, where it also transports and clears amyloid-beta.[c] [29] [30]

Beyond the Gene-Environment Dichotomy: Gene-Environment Interactions

Health and disease in the brain, as in any organ system, are influenced by multiple factors. By tradition, these factors are typically divided into genetic and environmental influences. In some cases, where a genetic or environmental influence is truly determinative, this dichotomy holds up.[d] More often, however, genetic and environmental influences interact.[e]

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[b] *The increased risk was relative to the more common ApoE3 genotype.*

[c] *ApoE in the brain is produced by astroglia and microglia, and ApoE receptors are expressed by neurons.*

[d] *An example is infantile Tay Sachs Disease, which is caused by a genetic error in fatty acid metabolism and is invariably fatal within the first few years of life.*

[e] *This is illustrated by the PKU (phenylketonuria) gene, which causes mental retardation in the context of a conventional diet. Importantly, by removing the amino acid phenylalanine from the diet beginning in infancy, (i.e. altering the environment), mental retardation is prevented.*

The ApoE4 gene provides an example of complex gene-environment and gene-gene-environment interactions. As mentioned above, ApoE4 increases risks for Alzheimer's and cardiovascular (among other) diseases, and Western lifestyle factors are emerging as key to these risks. This is illustrated in a 21-year Swedish observational study. It found that ApoE4 alone increased the risk for dementia/Alzheimer's disease by a factor of 2.83. When interactions with lifestyle factors were considered, the ApoE4-environment interactions increased the risk by a factor of 11.42. Environmental factors increasing risk included physical inactivity, alcohol drinking, smoking, and Western-type diet (specifically reduced intake of poly-unsaturated fat and increased intake of saturated fat). The authors concluded that lifestyle interventions may greatly modify dementia risk, particularly among genetically susceptible individuals.[31]

ApoE4 increases risks for Alzheimer's and cardiovascular diseases, and Western lifestyle factors are emerging as key to these risks.

A small body of cross-cultural epidemiologic studies also supports the view that Western lifestyle, including diet, is a key driver of ApoE4-associated risks. Several studies of Alzheimer's/dementia in Nigerian-Yoruba elders—who consume a low-fat, low-calorie, and predominantly plant-based diet[32] —found no significant association between ApoE4 and Alzheimer's/dementia. They also showed much lower age-adjusted rates of dementia/Alzheimer's disease. These findings contrasted sharply with the African-American control population in this study, which showed higher age-adjusted incidence of Alzheimer's and a significant association of ApoE4 with the disease.[33] [34] [35] [36] [37] [f]

Adding complexity, the ApoE-saturated fat interaction, mentioned above, can be further modified by additional genetic influences (for example, variations in an ApoE promoter gene).[38] Such gene-gene-diet interactions may explain inconsistent findings among previous studies examining ApoE4 as a risk factor for a variety of conditions. This also illustrates a more general point that the risk of many diseases is influenced by multiple genes and multiple environmental factors. These multiple factors constitute a virtual sea of conditions in which the influence of single factors may vary considerably.

Several large longitudinal studies have found that ApoE4 increases the risk of cognitive decline associated with atherosclerosis, peripheral vascular disease, and diabetes.[39] [40] Interestingly, one study examining the role of ApoE4 in chronic occupational lead exposure found that ApoE4 increased the adverse effect of lead on neurobehavioral function, including memory.[41] Each of these factors will be discussed below.

[f] *While the two populations had similar ApoE gene frequencies, the influence of other genetic factors cannot be ruled out as contributing to the different Alzheimer's/dementia rates in these two populations.*

Thus the effects of ApoE4 on the risks of Alzheimer's disease/cognitive decline increasingly appear to be influenced by environmental factors. The data suggest that modifying environmental factors may prevent the risks associated with ApoE4 and potentially a major portion of the Alzheimer's/dementia burden. Additional studies, discussed below, provide abundant evidence of environmental influences independent of ApoE4-related mechanisms as well.

We now turn more specifically to environmental contributions to Alzheimer's/dementia and cognitive decline.

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Environmental Chemicals

Relatively few studies have examined the influence of toxic chemical exposures on the risk of dementia/cognitive decline. Nonetheless, evidence has begun to develop. Studies implicating lead, pesticides, PCBs, particulate air pollution, and aluminum have recently been published. In one recent study, 21 percent of more than a thousand patients presenting to a university clinic for cognitive disorders had histories suggestive of toxic environmental and occupational exposures. A history of toxic exposure significantly lowered the age of onset of cognitive decline, an effect equivalent in magnitude to that caused by carrying two copies of the ApoE4 gene.[42]

Lead

Lead is toxic to multiple organ systems, including the brain. Low-level lead exposures can impair cognitive function in children. Evidence indicates there is no exposure threshold below which harmful effects do not occur. Extensive evidence also shows that past adult lead exposure in the work setting increases the likelihood of cognitive impairment.[43] [44] More recently low-level cumulative exposure to lead outside of the work setting has been shown to adversely affect cognitive function including visual-spatial/visual-motor function, language, processing speed, executive function, verbal memory and learning, and visual memory.[45] One longitudinal study divided a population of elderly men into four groups (quartiles), based on the amount of lead found in patella bone. It found each quartile increase in bone lead was associated with approximately five years of additional cognitive aging as measured by the Mini-Mental Status Exam. This suggests that lead has a substantial impact on cognitive aging across the population. [46]

A variety of mechanisms may contribute to lead neurotoxicity. In its various forms, lead can cross the blood-brain barrier, disrupt

calcium-dependent enzymes and neurotransmitter metabolism[47] and release, and cause neuronal oxidative stress[48] and aggregation of amyloid-beta .[49] In addition, lead impairs synaptic transmission and plasticity,[50] oxidative phosphorylation, glucose oxidation, and microtubule synthesis,[51] among other effects. Lead has also been shown to preferentially affect the prefrontal cerebral cortex, hippocampus, and cerebellum.[52]

Another mechanism has recently been proposed whereby early-life lead exposure may contribute to late-life neurodegeneration. The mechanism—referred to as Latent Early-Life Associated Regulation, or LEARn—is suggested by a series of studies by Basha, Zawia, and others in rodents and monkeys. LEARn is an example of a more general phenomenon whereby early life conditions predispose to adult disease. In this instance, exposing fetal rodents to lead caused brief increases during neonatal life in key Alzheimer's disease–related proteins. This was followed by delayed over-expression of these proteins and amyloid-beta in late life—long after early lead exposure had ceased. Interestingly, exposure to lead during old age did not cause increases in the Alzheimer's disease–related proteins.

These data suggest that early developmental lead exposure may lead to increased expression of amyloid precursor protein later in life, increasing amyloid-beta production.

Recently the same delayed, late-life increase in Alzheimer's disease–related proteins was reported in aged monkeys exposed in infancy to low levels of environmental lead. In addition, these monkeys showed Alzheimer's (amyloid) plaques in the frontal association cortex, an Alzheimer's disease–related brain region, as well as biochemical evidence of epigenetic imprinting.[g] [53] Taken together, these data suggest that early developmental lead exposure may lead to increased expression of amyloid precursor protein later in life, increasing amyloid-beta production.[54] [55] While lead's role as a developmental toxicant has been evident for nearly a century, the neurodegenerative toxicity of lead in the brain[h] has only come into focus in the past decade or so. Thus, lead may now be considered a lifecycle neurotoxicant.

Aluminum

Dietary exposure to aluminum salts is nearly universal in the developed world as they are commonly added to commercially prepared foods and beverages. They are sometimes used to clarify drinking water, make salt free-pouring, color snack and dessert foods, and make baked goods rise.[56]

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[g] *The evidence of epigenetic imprinting included decreased DNA methyltransferase activity and higher levels of oxidative damage to DNA.*

[h] *It has long been known that lead causes impairment of peripheral nerves, which are outside of the brain.*

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The possible role of aluminum in Alzheimer's disease/dementia has been debated since 1965 when controversial evidence emerged showing that aluminum injections into the brain caused neurofibrillary tangle–like pathology. (The relevance of this data to human disease is questionable, given the high dose and route of exposure.)

Several studies conducted in recent years have resurrected old questions about the potential for aluminum to contribute to neurodegenerative disease. One recent small pilot study in rats showed that chronic exposure to dietary aluminum at doses within the range of the human exposure spectrum was associated with aluminum accumulation in hippocampal neurons.[57] A larger follow-up study in rats showed a dose-response relationship between dietary aluminum and memory loss. [58] The exposure level at which memory loss began to increase (0.49 mg aluminum/kg/day) was well within the range of human dietary exposure. Though estimates vary, one exposure study found that half of Americans ingest 0.34 mg aluminum/kg/day or less, 45 percent ingest 0.34–1.36 mg/kg/day, and 5 percent take in more than 1.36 mg/kg/day as additives in commercially processed foods and beverages.[59] A recent analysis of aluminum content of foods found that some varieties of baking powder, pancake/waffle mixes and frozen products, and ready-to-eat pancakes contained the most aluminum of foods tested. The aluminum contained in a single serving of some pancakes [60] [61] (up to 180 mg of aluminum, or 3 mg/kg for a 60 kg person), was the equivalent of five times the dose associated (when ingested chronically) with older-age memory loss in the rat study.[i] [62] This suggests that consuming the high-aluminum varieties of these foods on a daily basis could lead to exposures well above the level at which age-associated memory loss was observed in the rat study.

In another study, brain specimens from rats chronically exposed to high-end human levels of aluminum exposure showed microscopic changes commonly regarded as components of plaque and tangle formation.[j] [63] [64]

A recent laboratory study found that exposure of human neural cells to nanomolar concentrations of aluminum induced gene expression promoting inflammation and cell death, similar to that observed

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[i] *Since the determinants of aluminum absorption are not yet fully understood, it is difficult to predict the aluminum exposure from aluminum content of a meal.*

[j] *The brain histopathology of exposed rats included oxidative damage, inhibition of PP2A (protein phosphatase 2A) activity, hyperphosphorylated tau, and granulovacuolar degeneration. PP2A is a major phosphate-removing enzyme in the brain which is active against tau and neurofilament hyper-phosphorylation. Plaques and tangles per se do not develop in rats.*

in Alzheimer's disease.[k] [l] [65] While this supports a possible role for aluminum in Alzheimer's disease/dementia, the relevance of this laboratory observation to real world conditions is not yet established.

Thus, recent evidence reopens a debate and rekindles concerns that current dietary exposures to aluminum may increase the risk of dementia/Alzheimer's disease. It should be noted that aluminum absorption is complex and influenced by many factors—including pH, the molecular state of aluminum, other nutrients in the food, and possibly unidentified host factors.[66] [67] [68] Because the quantity of aluminum ingested is not by itself a predictor of aluminum absorption, identifying safe dietary limits is difficult. Nonetheless, the new animal data and current dietary levels of aluminum exposure create an urgent need for additional research and dietary guidelines. Both the European Food Safety Authority and the Joint Food and Agriculture/WHO Expert Committee on Food Additives recently lowered their recommended safe upper limit (provisional tolerable weekly intake) for aluminum from 7 mg/kg/week to 1 mg/kg/week.[69] [70] This new limit is 7 times more protective than the current US recommended limit (minimal risk level) of 1 mg/kg/day.[71]

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Iron, Copper, Zinc

Iron, copper, and zinc are biologically essential and are normally present in the brain, although their levels are fairly tightly regulated through mechanisms that are not well understood.[72] [73] In addition, iron accumulates in the same areas of the brain in which the amyloid-beta peptide accumulates.[74] When controls fail, these metals can increase oxidative stress by catalyzing the production of free radicals directly[75] or by binding amyloid-beta and thus catalyzing the production of free radicals.[76] While the links among metals, oxidative stress, and amyloid-beta provide plausible general mechanisms whereby these metals may cause neurodegenerative disease, few details are known. In addition, few epidemiologic studies have examined the possible contribution of biologically essential metals to Alzheimer's disease/dementia. (See chapter 8 for discussion of Parkinson's disease risk.)

Air Pollution

While air pollution is often thought of as harmful mainly to the lungs, a large body of evidence indicates that the cardiovascular system is also vulnerable to the effects of air pollution.[77] Emerging evidence suggests that air pollution contributes to brain inflammation

[k] *This study used DNA microarray data.*

[l] *Increased expression was observed for: NF-kB subunits, IL-1B precursor, cytosolic phospholipase A2, cyclooxygenase 2, and amyloid precursor protein).*

A growing body of evidence has begun to link air pollution with neurodegenerative disease.

and the risk of Alzheimer's-type neurodegenerative disease as well.

Air pollution is a complex mixture of gases (notably ozone, carbon monoxide, and nitrogen and sulfur oxides), metals (e.g., lead, manganese), volatile organic compounds from industrial and vehicular sources, particulates, and lipopolysaccharide (LPS), among other constituents. While many of these components have been linked with illnesses, recent evidence incriminates particulate matter in a variety of diseases in several organ systems.[78] Particulates are a complex mix of solids and liquids (including organic and elemental carbon, nitrates, sulfates, and metals) in various sizes ranging from a few nanometers (billionths of a meter) to 10 microns (millionths of a meter) in diameter. The major human source of air pollution in the modern world is the burning of fossil fuels in motor vehicles and by industry.[79]

Studies demonstrate a variety of cardiovascular effects from both short- and long-term exposures to particulates—even at present day levels—including reduced oxygen supply to the heart (myocardial ischemia) and heart attacks, heart failure, stroke, arrhythmia and sudden death, cardiovascular hospitalization and mortality, and venous thrombosis (blood clots).[80 81]

While the risk to any one person from air pollution at a given point in time is small, the pervasive, constant nature of the exposure results in profound health impacts on the population as a whole. Though the full extent of the consequences of air pollution are still uncertain, known adverse impacts on health already place the particulate component alone as the thirteenth leading cause of global mortality, causing approximately 800,000 deaths per year.[82]

A growing body of evidence has begun to link air pollution with neurodegenerative disease. This evidence includes human and animal studies that combine histopathology, neuroimaging, cognitive testing, and limited epidemiology. Much of this evidence is drawn from recent postmortem studies comparing brain tissue from lifelong residents of cities with severe air pollution with brain tissue from lifelong residents of low-air-pollution cities. (All of the individuals in the studies had been free of neurologic disease or symptoms before death, and had died sudden, non-neurologic deaths.) These studies showed evidence of inflammation and Alzheimer's type brain tissue pathology in the residents of polluted-air cities, compared to the residents of relatively clean-air cities. The pathology included numerous

inflammatory markers,[m] accumulation of amyloid-beta[n] (one of the key protein markers of Alzheimer's disease), inflammatory activation of endothelium (the cells lining the inside of blood vessels), oxidative stress, and inflammatory cells.[83] [84]

Particulate matter has been seen in red blood cells (erythrocytes) in blood vessels within the brain[o] [85] (and other organs), and in inflammatory cells within brain tissue surrounding the blood vessels.[86] The studies also showed disruption of the blood-brain barrier in residents of polluted-air cities, potentially allowing inflammatory mediators and ultrafine air pollution particles access to the brain from the bloodstream.[p] In addition, ultrafine pollution particles were identified in olfactory bulb neurons, a potential conduit for selected toxicants to travel from the nose to the brain[q] without the interference of the blood-brain barrier.[87] Whether particulate matter or other toxicants can actually move from the olfactory bulb to other areas of the brain in humans is not yet known. [88] [89] [90] This question is of particular interest because some olfactory pathways lead to areas of the brain that are key to learning and memory (including the entorhinal cortex and the amygdala).[91]

Exposure to air pollution is associated with neuroinflammation, an altered innate immune response in the brain, and accumulation of amyloid-beta.

Ultrafine particles that penetrate deeply into the lungs initiate an inflammatory response and may be absorbed directly into the circulating blood.[r] [92] Similarly, particle deposition in the nose causes inflammation and disruption of the olfactory barrier—potentially facilitating the transport of toxicants into the olfactory bulb.

Amyloid-beta was seen in 100 percent of young carriers of the ApoE4 gene (genotype ApoE4/3) from highly polluted areas, compared with 58.8 percent of ApoE3/3 subjects.[s] [93] This suggests that people carrying ApoE4 may be more susceptible to inflammatory neurodegeneration associated with air pollution. Alpha-synuclein, a

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[m] *Inflammatory markers included increased COX2 expression, IL-1B, and CD14.*

[n] *Amyloid-beta accumulation was documented in the frontal cortex, hippocampus and/or olfactory bulb.*

[o] *Inflammatory mediators—such as TNF-alpha or IL-1B—in the blood or endothelium can be transmitted across the blood-brain barrier into the brain.*

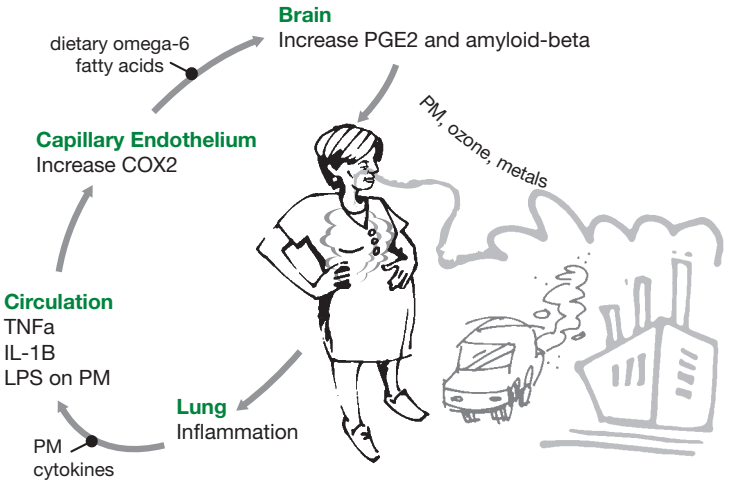
[p] *Ultrafine particulates are <100 nm in diameter. Only these very tiny particulates are small enough to pass from the lung into the bloodstream, and from there to potentially cross the blood-brain barrier.*

[q] *The olfactory pathway provides access in particular to areas of the brain that are critical for learning and memory.*

[r] *Particulate air pollution is highly inflammatory at the level of the lung and brain due to several inflammatory components. These components include bacterial lipopolysaccharide, known to stimulate the innate immune response (via toll-like receptors, as discussed in chapter 6). Particulate air pollution also contains combustion-derived heavy metals such as nickel and vanadium, which can also provoke inflammatory responses.*

[s] *Two-thirds of non-ApoE4 subjects from Mexico City showed amyloid-beta staining, compared to none of the non-ApoE4 subjects from non-air polluted cities.*

From the Smoke Stack to Your Brain
Air Pollution is Linked to Brain Inflammation & Amyloid-Beta Deposition



This diagram represents some of the pathways and mechanisms through which air pollution is thought to have inflammatory and degenerative effects in the brain. The diagram is not intended to be a comprehensive or literal representation of these processes. *(PM=particulate matter)*

pathological marker of Parkinson's disease, was also seen at a relatively high rate (23.5 percent) in young subjects from polluted cities. (See chapter 8.)

The authors concluded that exposure to air pollution is associated with neuroinflammation, an altered innate immune response in the brain, and accumulation of amyloid-beta as well as alpha-synuclein starting in childhood. They suggest that exposure to air pollution should be considered a risk factor for Alzheimer's and Parkinson's diseases. They also note that the ApoE4 gene may increase the risk of developing Alzheimer's disease in an air-polluted environment.[94]

In a separate study, children from highly polluted Mexico City, compared with controls from a low-pollution city, showed a high incidence of cognitive deficits on psychometric testing as well as brain abnormalities in the prefrontal region on MRI.[t] Similar MRI lesions were found in dogs from highly polluted areas. The lesions were associated on postmortem exam with neuroinflammation, ultrafine particulate matter deposition, and gliosis (proliferation of astrocytes, indicating neuronal injury).[95] [u] This suggests that brain inflammation linked with air pollution begins at an early age and is associated with early cognitive impairment. It should be noted that these studies do not tell us which air pollutants are responsible for the observed effects.

Animal studies with allergic[96] [v] or genetically vulnerable[97] [w] mice have demonstrated increased brain inflammation following short-term exposure to concentrated air particulates.[x] Each of these conditions facilitates the breakdown of respiratory epithelium by air particulates or other pollutants. When this barrier is disrupted, inflammatory mediators and particulate matter can more easily pass through to the systemic circulation, thereby facilitating access to the brain.[98]

Inside the brain, inflammatory cytokines activate microglia, a potent agent of neurodegeneration.[99] Elevated cytokines have also

[t] *The MRI abnormalities were white matter hyperintense lesions.*
[u] *These abnormalities were also associated with subcortical vascular pathology.*
[v] *Allergic airway sensitivity in this model was induced by sensitizing the mice to inhaled ovalbumin.*
[w] *Mice that are genetically modified to lose their ApoE gene (so-called ApoE knockouts) have increased oxidative stress.*
[x] *The exposure took place for two to five weeks, lasting 15-20 hours/week.*

been found to increase the expression of an enzyme (COX2) in the capillary lining (endothelium) of the brain, which produces the highly inflammatory prostaglandin, PGE2. Recent evidence links PGE2 with stimulation of amyloid-beta production, providing another possible mechanism that may connect inflammatory particulate air pollution with Alzheimer's disease.[y] [100] [101] [102]

Since PGE2 is derived from omega-6 fatty acids, the relatively high omega-6 fatty acid content of the Western diet (along with the low omega-3 content) may intensify PGE2 production, increasing amyloid-beta formation and the risk of Alzheimer's disease. The influence of omega-3 and omega-6 fatty acids in neurodegenerative disease is discussed further in the nutrition section below.

This evidence is consistent with the established link between air particulates and inflammatory injury to the lung, nose, blood vessels, and heart. These studies suggest that air pollution causes inflammation in the brain[z] and is likely to be contributing to the high prevalence of neurodegenerative diseases in the modern world

This evidence is consistent with the established link between air particulates and inflammatory injury to the lung, nose, blood vessels, and heart.

PCBs and Persistent Organic Pollutants

PCBs are industrial chemicals that were used for many years in a variety of applications, including as paint additives, lubricants, and insulators in electrical equipment. They were banned from production in 1977 in the US because of evidence that they could cause cancer. Subsequently, PCBs were found to interfere with normal brain development and thyroid hormone function.[103] PCBs continue to contaminate the general environment because they are persistent and not easily broken down. Since they are fat soluble and bioaccumulative, they also contaminate the general food supply though levels have been falling. Biomonitoring data from the Centers for Disease Control show that human PCB levels in the general population have also been falling since the ban, though they remain a contaminant of concern.

While there is extensive epidemiology demonstrating the toxicity of PCBs on the developing brain, to our knowledge only three published epidemiologic studies have explored the effects of PCBs on cognitive decline/dementia in older subjects. These studies looked at PCB exposure in three different settings—an oil contamination/poisoning incident (Yucheng), environmental exposure through fish consumption, and a group of occupationally exposed workers. Each study demonstrated

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[y] *PGE2 stimulates amyloid-beta by increasing expression of gamma secretase, one of the enzymes involved in producing amyloid-beta .*

[z] *Particulates and/or inflammation are noted in blood vessels as well as the tissue of the brain.*

an association of adult PCB exposure with dementia/cognitive impairment. While PCB exposures in the oil contamination and occupational studies were relatively high, the exposures in the fish consumption study are closer to those in the general population.

One of these studies tested cognitive abilities in older adults who had been exposed to cooking oil contaminated with PCBs and PCDFs (another persistent organic pollutant) more than 20 years earlier. The study found, among women, significant dose-dependent reductions in attention and memory functions.[aa] [104] Another of these studies found older subjects who regularly consumed Great Lakes fish had impairments in memory and learning compared to controls.[ab] [105] While each of these studies included additional contaminants, the contaminants were different in the two studies and the findings for PCBs were comparable. The third investigation, a retrospective study of over 17,000 PCB-exposed workers showed an excess of dementia mortality among women most highly exposed.[106] [ac] These studies are consistent with prior research showing deficits in memory and learning in children exposed to PCBs before birth or in infancy.[ad] Animal studies as well have shown that exposure to various forms of PCBs reduced learning ability and spatial discrimination among other cognitive impairments.[107-109] The epidemiological studies described are limited by their case-control design. Since they are not longitudinal, prospective studies, they cannot establish when the cognitive decline occurred.

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Several epidemiologic and laboratory (in vitro) studies have linked exposure to PCBs as well as other persistent organic pollutants to inflammation, diabetes,[110] [111] and metabolic syndrome.[112] Low-dose PCBs have also been linked to atherosclerosis[113] and obesity.[114] Since these diseases are themselves risk factors for dementia/cognitive decline, PCB effects on cognitive decline/dementia might be mediated in part through these risk factors, as well as through direct PCB effects on the brain. These studies also provide further evidence that environmental chemicals can increase the risk of other diseases in the Western disease cluster.

The mechanisms whereby PCBs may cause neurodegeneration are not well understood.[115] Some kinds of PCBs interact with the aryl hydrocarbon receptor (AhR), activating a family of enzymes (cytochrome P450 1A1 subfamily) that lead to oxidative stress and

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[aa] *The study was a retrospective cohort investigation involving 162 subjects 60 years of age or older who had been exposed in the Taiwan oil contamination epidemic of 1979.*

[ab] *The cohort study included 101 consumers of Lake Michigan fish, ages 49-86 years of age.*

[ac] *Standardized mortality ratio = 2.04. PCB exposure in this study was estimated by history.*

[ad] *Other developmental effects of PCBs in children include impaired attention and IQ and hyperactivity. (See* In Harm's Way: Toxic Threats to Child Development *p.78)*

free-radical production.[116] Various PCBs have also been linked to inflammatory activation of endothelial cells (a process linked to atherosclerosis),[117] and to the impairment of long-chain fatty acid synthesis.[ae] [118] Since inadequate levels of long-chain fatty acids are implicated in dementia and cognitive decline (see the nutrition section below), the inhibition of long-chain fatty acid synthesis by PCBs may provide another plausible mechanism by which PCBs may promote cognitive decline/dementia. PCBs also affect the function of thyroid hormone, which is implicated in cognitive impairment as well.[119] [120]

Pesticides

A growing body of evidence demonstrates neurologic impacts at lower levels of chronic exposure to neurotoxic pesticides in adults, primarily in the occupational setting.

Pesticides are used extensively in the United States and throughout the world. The licensing of over 18,000 American pesticide products and the application of over two billion pounds of pesticides per year to crops, homes, schools, parks, and forests creates the potential for pervasive human exposures.[121] [122]

Many pesticides exert their killing effects through neurotoxic mechanisms. Historically, most attention was focused on acute effects to humans from relatively large exposures, but in recent years neurological effects from chronic, low-level exposures have been more widely studied in laboratory animals, people who apply pesticides, and the general public. Toxicologists and epidemiologists have been particularly interested in the neurodevelopmental impacts of the organophosphate family of insecticides because of their widespread use and resulting human exposures.[123] Animal and epidemiologic studies of the neurodevelopmental impacts of organochlorines, carbamates, and pyrethroids are less extensive.

Acute high-dose effects of organophosphates include headache, dizziness, nausea, vomiting, papillary constriction, sweating, tearing, and salivation. Severe poisoning may progress to seizures, arrhythmias, coma, and death. Many studies (reviewed in Kamel and Hoppin[124] and others[125]) have documented chronic, lingering symptoms following acute high-dose organophosphate exposure, including cognitive and psychomotor impairment, motor dysfunction, and reduced vibration sensitivity.[126] [127] [128]

Though studies are not fully consistent, a growing body of evidence demonstrates neurologic impacts at lower levels of chronic exposure to neurotoxic pesticides in adults as well, primarily in the

[ae] *Fatty acid metabolism is thought to be impaired due to PCB inhibition of the delta 5 and 6 desaturase enzymes, preventing the elongation of fatty acids.*

occupational setting.[af] [129] These impacts include neurobehavioral performance impairments and sensory, motor, and nerve dysfunction. As noted in Kamel and Hoppin, most (though not all[130] [131]) studies examining cognitive and psychomotor function have documented chronic impairments in association with long-term, lower-dose occupational pesticide exposure. [132] [133] [134] Cognitive domains that are affected include memory, attention, visual-spatial processing, pattern memory, and others. Most of these were studies of organophosphate exposures, though a few examined the organochlorine DDT and fungicides. For example, chronic low-level exposure to fungicides among French vineyard workers increased the risk of poor performance on tests of selective attention and working memory by a factor of 3.5. Tests of associative memory, verbal fluency, and abstraction were similarly impaired.[135]

Several studies have also found an increased risk for Alzheimer's disease or dementia in association with occupational pesticide exposure.

Several studies have also found an increased risk for Alzheimer's disease or dementia in association with occupational pesticide exposure.[136] A six-year prospective study of 1,507 elderly people in France found that a history of occupational exposure to pesticides increased the risk of developing Alzheimer's disease by a factor of 2.39. An increased risk was not seen in agricultural occupations more generally.[137] Another five-year longitudinal, population-based study in Manitoba found that a history of occupational exposure to fumigants/defoliants was associated with a 4.35-fold increased risk of Alzheimer's disease.[138] Several studies have also failed to find associations of pesticide exposure with Alzheimer's disease.[139] [140]

Very few studies have looked for chronic cognitive effects of pesticide exposure in adults outside of the occupational setting. One of these studies conducted in the Netherlands found that gardeners (as well as farmers) had an increased risk of having mild cognitive dysfunction at the outset of the study, as well as an increased risk of developing mild cognitive dysfunction over the three-year course of the study.[141] Another study looking for an association of non-occupational exposure to pesticides (based in part on records of herbicide and insecticide spraying and areas of residence) failed to find a link.[142] The authors of this study noted several methodologic problems – including the use of retrospective exposure assessment and proxy respondents – that might have reduced the ability of the study to recognize an association if it did exist.

[af] *Several issues in research methods contribute to the difficulty demonstrating the cognitive effects of pesticides at lower exposure levels. Notably, accurate prior exposure is especially difficult to determine in the absence of good biomarkers of cumulative exposure for most pesticides. Instead, exposure is generally assessed by history or occupational category. Since such methods typically provide imprecise estimates of exposure, the findings of such studies tend to under-recognize neurotoxic (and other) associations with low level pesticide exposure, (Type II error). This under-recognition of actual associations, it should be noted, does not undermine the validity of any associations that are observed. (Kamel and Hoppin 2004)*

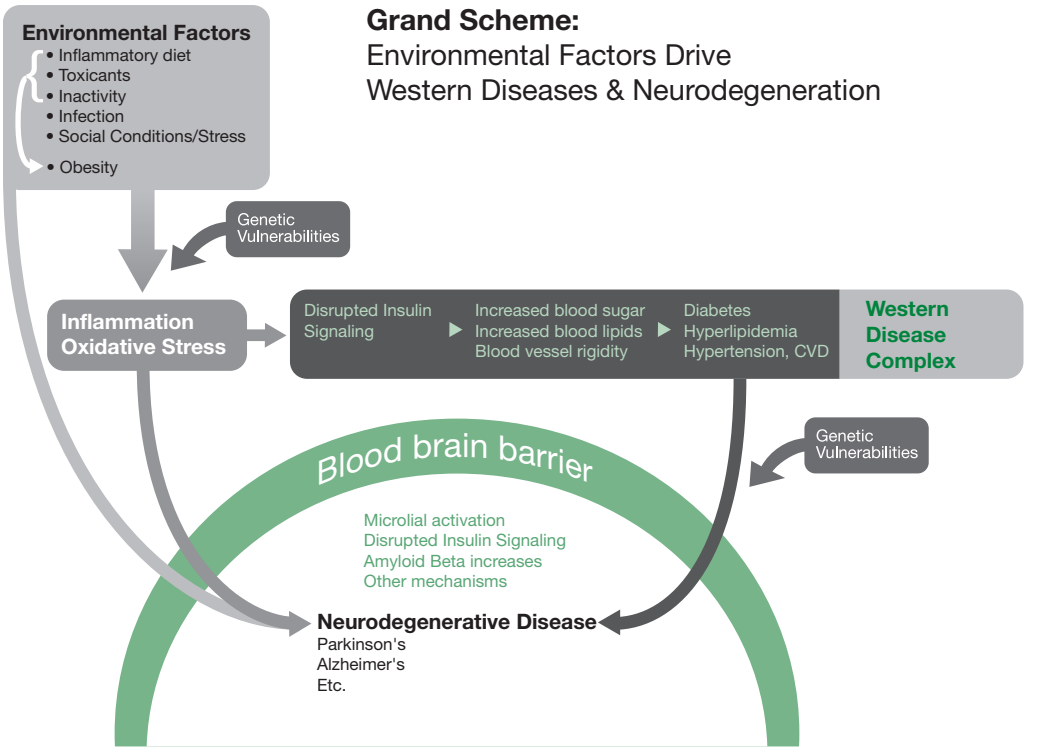
In summary, many but not all studies find that acute high-dose and chronic lower-dose occupational exposures to some neurotoxic pesticides are linked to an increased risk of cognitive decline, dementia or Alzheimer's disease. Data on the effects of chronic non-occupational exposure are too sparse to allow any conclusions. Research attempting to link chronic non-occupational pesticide exposures and cognitive impairment is especially hampered by the difficulty of distinguishing exposed from unexposed subjects (due in part to the lack of long-term exposure biomarkers). This difficulty leads to exposure misclassification, which makes associations with low-dose exposure very hard to identify even if they do exist.

The Western disease cluster and Alzheimer's disease/dementia can be seen in part as consequences of inflammation and the associated disruption of insulin signaling.

Links to Western Disease Cluster and Inflammatory Markers

Substantial epidemiologic evidence suggests that diseases that co-occur in the Western disease cluster are also risk factors for Alzheimer's disease/dementia and cognitive decline. The evidence is strongest for diabetes but is also substantial for midlife hypertension, obesity and elevated total cholesterol.

While each of these diseases is linked to Alzheimer's disease/dementia through multiple mechanisms, inflammatory disruption of insulin signaling provides an emerging common denominator and serves



as a framework as shown in the figure below. (Also see chapter 6 sections on the Insulin and Toll-Like Receptors cascades.) The backbone of this framework consists of inflammatory signaling—triggered by a variety of environmental factors and gene-environment interactions—and the resulting disruption of insulin signaling. Disrupted insulin signaling in turn causes the metabolic and vascular consequences of diabetes: hyperglycemia (elevated blood sugar), hyperlipidemia (elevated blood lipids), and vascular disease. Since inflammation—and the associated oxidative stress—can be transmitted across the blood-brain barrier, systemic inflammation/oxidative stress is also associated with brain inflammation/oxidative stress. These in turn are important drivers of neurodegeneration. Inflammatory disruption of insulin signaling in the brain may contribute to abnormalities that are commonly observed in Alzheimer's disease, namely impairments in glucose metabolism and the synthesis of acetylcholine (a neurotransmitter whose production requires byproducts of glucose metabolism). Thus the Western disease cluster and Alzheimer's disease/dementia can be seen in part as consequences of inflammation and the associated disruption of insulin signaling.

Several large prospective cohort studies found that diabetes was associated with a greater risk of developing cognitive decline and dementia.

Though not all studies are consistent,[ag] an extensive and growing body of epidemiologic literature suggests the association of the Western chronic disease cluster illnesses with increased risks for Alzheimer's disease/cognitive decline. One illustrative study (following over 1,400 middle-aged subjects for more than 20 years on average) found that midlife obesity, high total cholesterol, and elevated systolic blood pressure were all significant risk factors for dementia, each increasing the risk by approximately two-fold. The study also found the risks were additive, increasing the risk for dementia 6.2-fold when all factors were present.[143] Below we focus on studies examining diabetes/hyperglycemia, obesity, metabolic syndrome, and increased inflammatory markers as risk factors for Alzheimer's disease/cognitive decline.

Diabetes/hyperglycemia

Several large prospective cohort studies found that diabetes was associated with a greater risk of developing cognitive decline and dementia. A review of these studies estimated that diabetes increased the risk of Alzheimer's disease by 50–100 percent and of vascular dementia by 100–150 percent.[144] [145] Interestingly, a four-year prospective study of older women found the adjusted risk of developing cognitive impairment is increased not only among diabetics (1.79-fold), but also among those with minimally impaired glucose tolerance,

[ag] *See below for specific examples.*

defined as fasting glucose greater than 110 mg/dL (1.64-fold).[146] Similarly, a large 10-year prospective study of nondiabetic women found that elevated fasting insulin levels also predicted faster decline in scores of verbal memory ability and cognition.[ah 147] Higher C-peptide levels, (indicating increased insulin secretion, which is characteristic of insulin resistance and type II diabetes), were also found to be predictive of cognitive decline in older women without diabetes in the Nurses Health Study.[148] This evidence of a link between hyperinsulinemia and accelerated cognitive decline supports the hypothesis that insulin resistance (associated with inflammation and hyperinsulinemia) is an important contributing cause of cognitive decline and Alzheimer's disease. Other mechanisms by which diabetes/hyperglycemia may increase the risk for Alzheimer's disease/cognitive decline include neuronal damage from increased oxidative stress and advanced glycation end products (amino-sugar compounds that are increased in hyperglycemia and contribute to oxidative stress); reduced acetylcholine production resulting from reduced glucose availability;[149] and insulin effects on amyloid-beta metabolism and vascular disease.[150]

At least three studies have found an association between increased body mass index and cognitive impairment or decline.

Several studies have reported an interaction between diabetes and ApoE4 that increases the risk of developing Alzheimer's disease. One of these studies reported the risk of Alzheimer's disease increased by a factor of 4.58 among diabetics carrying the ApoE4 gene.[151 152]

Obesity

Numerous large prospective epidemiological studies have found midlife obesity to be associated with greater risk of dementia in later life[153-158] (though not all studies are consistent[159 160]). For example, a 27-year prospective study of over 10,000 men and women in the Kaiser Permanente Medical Group found that people who were obese in midlife had a 74 percent increased risk of dementia later in life, while overweight people had a 35 percent increased risk.[161] At least three studies have found an association between increased body mass index (BMI) and cognitive impairment or decline.[162 163] For example, in a study of more than 2,200 healthy workers 32–62 years of age, higher BMI was associated with both lower cognitive scores at baseline and greater five-year cognitive decline.[164] Another cross-sectional study in adults 54–81 years old found the combination of

[ah] *Cognitive status was determined by the Telephone Interview for Cognitive Status.*

greater waist circumference (or BMI) and higher blood pressure was associated with reduced executive function, manual dexterity, and motor speed. [165]

Providing further support for the view that midlife obesity increases risks for cognitive decline, three recent imaging studies showed obesity in middle-aged and older adults was associated with a number of abnormalities in brain structure. Those abnormalities included reduced hippocampal[166] and total brain volumes,[167] increased white-matter hyperintensities[168] (areas of increased signal intensity on MRI exams, thought to reflect small-vessel vascular disease),[169] and temporal lobe atrophy.[170]. Another imaging study found reduced levels of markers of neuron viability (n-acetylaspartate) and membrane metabolism (choline metabolites) in middle-aged subjects with increased BMI. These abnormalities were particularly evident in the frontal lobe, an area of the brain especially prone to damage during aging. These findings underscore concerns that obesity may contribute to abnormalities in brain structure and function in midlife, laying the groundwork for cognitive decline or dementia in later life.[171]

Metabolic Syndrome, Inflammation, and Oxidative Stress

An increase in one or more inflammatory markers is itself a risk factor for cognitive decline/ dementia.

Several[172-175] but not all[176] studies have found metabolic syndrome to be a risk factor for developing Alzheimer's disease/cognitive decline. One of these found metabolic syndrome a significant risk factor specifically in the presence of increased inflammatory markers.[177]

An increase in one or more inflammatory markers is itself a risk factor for cognitive decline/dementia. Fully ten out of eleven large population-based prospective studies have shown positive associations between inflammatory marker elevations and subsequent cognitive decline or dementia/Alzheimer's disease.[178-187] While different studies have found different markers to be associated with increased risk,[ai] the consistent finding of an increase in one proinflammatory marker or another across different populations is notable. The one prospective study that did not find an association used a less sensitive outcome measure (a one-time measure of cognitive function rather than decline across two or more points in time[aj]). This may have reduced the ability of the study to detect an effect if present.[188] [ak] The association of increased inflammatory markers with cognitive decline/dementia is

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[ai] *The different markers found to be associated with cognitive decline/dementia may reflect both differences in study characteristics (experimental design and measurement techniques) as well as potential differences in the populations studied (including different risk factors, nutritional profiles, toxicant exposures, and other poorly identified modifiers of inflammatory response).*

[aj] *Cognitive function is a one-time measure and does not account for baseline cognitive ability.*

[ak] *The study is ongoing and a report on the relation between CRP and cognitive decline is anticipated in the future.*

supported by the very large body of evidence pointing to inflammation as key in the pathogenesis of dementia. This includes histopathology, epidemiology, gene polymorphism studies, and links between inflammatory cytokines and microglial activation and amyloid-beta processing. (See chapter 6.)

While epidemiologic studies have not (to our knowledge) examined the role of oxidative stress in the development of Alzheimer's disease/cognitive decline, an interesting recent study did look at oxidative stress—as indicated by oxidized LDL-cholesterol levels—as a predictor of metabolic syndrome. It followed over 1,800 middle-aged adults for five years and found that oxidized LDL (determined at the outset of the study) predicted the development of metabolic syndrome in a dose-response fashion, with the highest quintile having a 3.5-fold increased risk of metabolic syndrome relative to the lowest quintile. Oxidized LDL also predicted the development of abdominal obesity, elevated fasting glucose, and high triglycerides.[al] [189]

…Social, mental, and physical activity are inversely associated with the risks of Alzheimer's disease/dementia and cognitive decline.

Social, Mental, and Physical Activity

A substantial body of evidence indicates that social, mental, and physical activity are inversely associated with the risks of Alzheimer's disease/dementia and cognitive decline. This includes long-term human observation and controlled animal studies. The animal studies provide important corroborating evidence for the human observational studies, which are subject to certain difficulties that we will explain.

A body of relevant animal research literature has emerged in the area of "environmental enrichment." This research demonstrates the relationship of cognitive performance—as measured, for example, by performance on the Morris water maze, a test of memory—to variations in the cage environment. The cage environment is varied by changing the number of objects available for exploration or the number of animals in the cage. Two important and consistent findings have emerged from this literature. First, and not surprisingly, rodents learn and remember better in an enriched environment. Second, neurogenesis (the creation of new nerve cells) is increased in an enriched environment, specifically in the hippocampus. One of the mechanisms reported to account for this remarkable finding is increased synaptic and dendritic growth. Other preliminary, as yet

[al] *Being in the highest (vs. lowest) quintile for oxidized LDL increased the risk of having abdominal obesity, elevated fasting glucose, high triglycerides, and metabolic syndrome by a factor of approximately 2.3.*

unreplicated findings include increases in brain-derived nerve growth factor and alterations in amyloid-beta levels.[190 191 192]

Human studies show analogous findings in the areas of social, physical, and mental activity. A recent review of 15 longitudinal studies found an increased risk of cognitive decline with reduced social networks (5 of 7 studies) and physical inactivity (6 of 7 studies). Increased dementia risk was also found in relation to reduced social networks (6 of 7 studies). While all studies were assessed as methodologically sound, the possibility that reduced social, mental, and physical activity is itself an expression, rather than a cause, of early dementia cannot be excluded.[am 193 194] Thus, animal studies showing the benefits of environmental enrichment provide important corroborating evidence. Specific findings of human studies include the following:

Engaging in leisure time physical activity at least twice a week in midlife was associated with a greater than 50 percent reduction in risk of dementia/ Alzheimer's.

- Substantial reductions were seen in the rate of cognitive decline among subjects with extensive social networks and social engagement, in a group of over 6,000 African-American and Caucasian elders followed for over five years.[195] (The rate of cognitive decline was reduced 39% in subjects with high social network ratings, and 91% in those with high social engagement ratings.)
- Engaging in leisure time physical activity at least twice a week in midlife was associated with a greater than 50 percent reduction in risk of dementia/Alzheimer's disease. This group was followed for more than 20 years.[196]
- Cognitive inactivity was associated with a 2.6-fold increased risk of developing Alzheimer's disease, a higher incidence of mild cognitive impairment, and more rapid decline in cognitive function in a group of more than 700 elders followed for up to 5 years.[197]

A growing number of studies have begun to clarify one mechanism in particular that may account for much of the pervasive benefits of exercise—for cognitive function as well as for cardiovascular disease, diabetes, and other components of the Western disease complex. In brief, these studies suggest that exercise transiently increases reactive oxygen species (free radicals), and then strongly up-regulates antioxidant capacity. The net effect is that people who exercise regularly have reduced ongoing levels of oxidative stress and inflammatory burden.[198-200]

[am] *The technical term for this problem is reverse causation.*

Psychosocial Stress

Social, mental, and physical activity also help moderate the effects of psychosocial stress—broadly defined as a variety of states associated with distress, namely depression, anxiety, social isolation, chronic life stress, personality traits, and other individual or community characteristics.[201] Psychosocial stress is well established as a risk factor in cardiovascular disease. While the role of psychosocial stress in dementia/cognitive decline is complex and incompletely understood, a growing body of evidence suggests an emerging key role in the development of dementia/cognitive decline.

Psychosocial stress is well established as a risk factor in cardiovascular disease.

Though relatively few epidemiologic studies have looked at the role of stress in neurodegenerative disease, the studies that do exist suggest that psychosocial stress has an important influence in the development of cognitive decline and dementia. Numerous studies suggest that depression is a risk factor for later development of Alzheimer's disease.[202] [203] Though some studies suggest depression is a very early (prodromal) symptom of Alzheimer's disease rather than a risk factor for the illness,[204] [205] a recent meta-analysis of 20 studies found that a history of depression approximately doubled the risk for the later development of Alzheimer's disease.[an] [206] Similarly, recent prospective cohort studies found the tendency to experience psychological distress was associated with a tenfold increased risk in episodic memory decline[ao] [207] and a 2.7-fold increased risk of developing Alzheimer's disease.[208] An anatomic basis for the association of stress and Alzheimer's disease/cognitive decline is suggested by observations that major depression and post-traumatic stress disorder are associated with smaller hippocampal volume,[209] [210] though not all studies are consistent.[211]

A substantial body of work describes multiple mechanisms linking stress with increased risk of Alzheimer's disease/cognitive decline. One key mechanism is provided in the hypothalamic-pituitary-adrenal (HPA) axis—or "stress circuit."[ap] This axis links depression, anxiety, or other stressors with a cascade of events involving the hypothalamus and pituitary in the brain (which increase corticotropin-releasing hormone [CRH] and adrenocorticotropin [ACTH], respectively) and the adrenal glands (which increase cortisol, epinephrine, and norepinephrine). These hormones increase blood pressure, heart rate, and blood

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[an] *The odds ratio was 1.9 in cohort studies, and 2.03 in case control studies.)*

[ao] *The 90th and 10th percentiles for being distress-prone were compared.*

[ap] *The HPA Axis hypothesis was developed by Drs. George Chrousos, Chief of Pediatric and Reproductive Endocrinoology at the National Institute of Child Health and Human Development, and Philip Gold of the Clinical Neuroendocrinology Branch at the National Institute of Mental Health. The theory is based on a large body of observational and laboratory data involving people and animals.*

sugar, among other effects. In addition, the sympathetic nervous system and a variety of other basic functions—including the immune and reproductive systems, growth, and gastrointestinal tract—are affected. Normally cortisol acts through a negative feedback loop to reduce CRH production, shutting down the stress activation after the threat has passed. In the presence of chronic stress, however, these hormones and systems are continually activated, contributing to risks for high blood pressure, elevated blood lipids, atherosclerosis, impaired growth in children, and reproductive dysfunction, among other effects.[212]

A variety of studies support a link between the HPA axis and Alzheimer's disease/cognitive decline. Animal[213] and/or human studies[214] have shown stressful experience or depression was associated with increased levels of adrenal corticosteroids, and that these hormones can damage the hippocampus (which has a high concentration of corticosteroid receptors[215]) and worsen damage from other neurological insults.[216] Some studies suggest that elevated blood cortisol levels are related to clinical progression of dementia/cognitive impairment.[217] [218] Further, stressful experience and depression themselves may be associated with structural changes in the hippocampus and impaired forms of learning and memory.[219] Providing additional support, recent studies in an Alzheimer's mouse model showed that isolation stress over three months increased amyloid-beta levels in brain interstitial fluid by 84 percent. Acute restraint stress increased amyloid-beta levels within hours, an effect that was mediated by CRH.[220] Isolation stress in this model has also been associated with impairment in memory function, decreased neurogenesis, and greater amyloid-beta deposition.[221]

Psychosocial stress has also been linked with elevated cytokine production.

Endothelial dysfunction provides another mechanism linking psychosocial stress with cardiovascular disease in animals and humans.[222] [223] Since vascular disease associated with endothelial dysfunction increases risks for dementia, the linkage of psychosocial stress to endothelial dysfunction may also contribute to cognitive decline/dementia.

Psychosocial stress has also been linked with elevated cytokine production. Several studies in people show that chronic stress increases age-related proinflammatory cytokine production.[224] One of these showed that the rise in IL-6 cytokine levels over a six-year period was four times greater in a group of 119 stressed spouses caring for partners with Alzheimer's disease than in non-stressed controls.[225] Another cross-sectional study of 43 older adults showed a similar relationship of higher cytokine levels in association with greater depressive symptoms.[226] Interestingly, higher ratios

of omega-6:omega-3 fatty acids in the blood increased the association of depression with cytokine levels in this study. In other words, the combined effect of depressive symptoms and higher omega-6:omega-3 ratios increased proinflammatory cytokine production beyond the effect of either variable alone.[aq] A similar pro-inflammatory effect of higher omega-6:omega-3 ratios was seen in the effects of exam stress on cytokine production (in stimulated blood specimens) in a group of 27 university students.[227] These and other studies underscore concerns about the potential aggravating role that high omega-6:omega-3 ratios in the American diet may play in promoting proinflammatory cytokine elevations in high-stress conditions.

Animal data also support the link between psychosocial stress and elevated cytokine production. Rats, for example, exposed to tail-shock stress prior to injection with LPS produced more proinflammatory cytokines, or produced them more rapidly, than did unstressed rats.[228] Studies in stressed mice and in cell culture identified noradrenalin (also known as norepinephrine) as the factor activating—in a dose- and time-dependent fashion—NFkB expression. This identifies a specific pathway by which stress (via sympathetic nervous system and HPA axis activation) may promote mononuclear cell activation—contributing to the development of cardiovascular and other chronic inflammatory diseases.[229]

Although studies have not yet—to our knowledge—examined the role of stress-induced cytokine elevations in the development of dementia/cognitive decline, a substantial body of prospective studies shows a consistent association of elevated cytokines with subsequent dementia/cognitive decline. (See "Metabolic Syndrome, Inflammation, and Oxidative Stress" above.)

Very few long term clinical studies have examined the potential effects of stress reduction on chronic diseases. One three-year randomized controlled clinical trial showed impressive benefits of stress management on important markers of cardiovascular risk in subjects with established ischemic heart disease. In addition to showing reduced depression and distress, subjects randomly selected to practice stress reduction had reduced ischemia and improved cardiac function during mental-stress testing, improved endothelial function (as measured by flow-mediated dilation) and enhanced autonomic activity (as indicated by improved heart rate variability and baroreflex sensitivity).[230 ar] Relaxation techniques have also been shown to reduce blood

Relaxation techniques have also been shown to reduce blood pressure by 5–10 mm in some subjects.

[aq] *Together these two factors accounted for accounted for 18% of the IL-6 and 40% of the TNF-*α*variance.*

[ar] *The stress management program consisted of 1.5 hours per week of instruction in stress management skills, muscle relaxation, and imagery techniques for 16 weeks.*

pressure by 5–10 mm in some subjects.[231] In addition, numerous uncontrolled, non-randomized, short term pilot studies suggest that a variety of stress reduction techniques (yoga, mediation, mindfulness based stress reduction) may be beneficial, and merit further investigation. These studies found improvements in various cardiovascular, immune, endocrine, autonomic and psychometric indicators after short term use of stress reduction techniques. Two large randomized trials did not find a benefit of stress management on cardiac morbidity and mortality. This may be due to the fact that the stress management did not reduce emotional distress.[232] [233]

In summary, psychosocial stress, an established risk factor for cardiovascular disease, is increasingly linked to cognitive decline/dementia. Chronic activation of the HPA axis, or stress circuit, appears to play a key role in mediating this risk, and is associated with hippocampal damage, elevated amyloid beta levels and dementia. Stress and HPA activation are also associated with increased cytokine production, which in turn has been associated with cognitive decline/dementia in a large body of studies. Clinical intervention studies are difficult to design and conduct, and few long term randomized controlled trials have been done to examine the effects of stress reduction on chronic illnesses of the Western disease complex. None the less, one three-year randomized controlled trial showed impressive benefits of stress management on important markers of cardiovascular risk in subjects with established ischemic heart disease.

Socioeconomic Status and Education

The relationship between socioeconomic status and dementia risk is complex and data are somewhat inconsistent. Difficulties arise because lower socioeconomic status is often associated with poor nutrition, lifetime exposures to environmental pollutants, less education, stress, and sometimes unhealthy behaviors. Most, but not all, studies show that less education is associated with an increased risk of dementia/Alzheimer's disease. One study shows that the higher risk of dementia associated with less education is independent of unhealthy lifestyle factors, such as smoking.[234] When education and socioeconomic status are each evaluated, less education seems to be the more important determinant of risk.[235] The combination of low socioeconomic status and elementary school–only education increased the risk of Alzheimer's disease threefold compared to people with high socioeconomic status and higher education. Some data also show that clinical symptoms of dementia appear earlier

in people of lower socioeconomic status when compared to people of higher socioeconomic status, including those with more objective evidence of brain volume loss and pathology on imaging.[236] These findings suggest that the combination of lower socioeconomic status and less education is a combination that may accelerate the onset of dementia/Alzheimer's disease and that increased brain reserve, associated with more education, may be somewhat protective.

Nutritional Factors

The critical importance of dietary factors is now recognized in the prevention and treatment of diabetes (particularly type II) and cardiovascular disease. [237] [238] Similarly, dietary factors are emerging as critical factors in cognitive function and brain aging. [239-241] Not unexpectedly, the dietary factors that reduce risks of diabetes and cardiovascular disease likewise likewise appear to reduce risks for cognitive decline/dementia.[242] While many studies have focused on single nutrients, combined effects of various nutrients and broad dietary patterns are also vitally important. This was illustrated in one epidemiologic study that found if only one "good" dietary habit—such as either omega-3 fatty acid or fruit/vegetable consumption—was present, it did not provide protection against the development of dementia. However, if these two "good" dietary habits were present, the risks were significantly reduced (hazard ratio 0.72). [243]

Difficulties Studying the Impacts of Nutritional Factors in Cognitive Decline/Dementia

Scientific studies examining the impacts of nutrition on disease risks are difficult to design and implement in a way that produces valid information. As a result, the existing literature is often ambiguous. Long ago, the field of nutritional science adopted the habit of studying the diet as a collection of nutrients that could be manipulated and examined one by one rather than as a complex mixture of relationships. Perhaps this approach gained currency when single vitamin deficiencies were discovered to cause specific diseases and fortification programs reduced or eliminated the problem. But whatever the reasons, this approach is also consistent with the general reductionist approach to science that dominated during the 20th century. More recent epidemiologic studies are beginning to study the impacts of various patterns of eating rather than of single foods or nutrients.

Whether focused on single nutrient or dietary patterns, clinical nutrition studies are inherently difficult for a number of reasons. For example, dietary exposure to various nutrients is usually estimated mainly through the use of food frequency questionnaires, which have substantial uncertainties. While biomarkers (such as omega-3 levels in the blood) may provide more reliable evidence of dietary consumption, such biomarkers of consumption are usually unavailable or unaffordable. Another problem is that the consumption of a given food (such as fish) also entails not eating other foods (such as fast food). It can be difficult to differentiate the effects of what is being eaten from the effects of what is not being eaten. Another difficulty is that long latencies for development of dementia require long duration for prospective studies, further driving up the cost of the study. Further, since food choices are often part of a pattern of broader healthy choices, it may be difficult to control for residual confounding by these other choices.

And finally, the gold standard for evidence—the randomized, controlled clinical trial—is virtually impossible to conduct, in part because it is very difficult to blind subjects to what they're eating. In addition, long-term dietary interventions are inconvenient and compliance requires an extraordinary effort on the part of subjects. Thus, there is a notable lack of long-term nutritional intervention studies in the area of dementia/cognition—as in other areas as well.

Consequently, the understanding of nutritional factors in cognition must derive from other forms of inquiry—human observation, brief clinical investigations, and animal intervention studies. Such data have allowed important conclusions to be drawn in the areas of diabetes and heart disease that are key to the prevention of these diseases, despite the obstacles to conducting long-term nutrition intervention studies.

The difficulty of defining and measuring dietary patterns and the lack of studies looking at multiple nutrient interactions limit the current database. Nonetheless, several general conclusions regarding nutritional influences of cognitive decline are supported by existing data. Here we briefly summarize some of the key conclusions.

Lipids

Not unexpectedly, the dietary factors that reduce risks of diabetes and cardiovascular disease likewise appear to reduce risks for cognitive decline/dementia.

Lipids are important building blocks in the brain. They provide the key constituent of nerve cell membranes as well as the substrate for myelin that wraps nerve axons, providing insulation to preserve nerve impulses as they flow from one cell to another. Lipids are also key players in immune system function. In particular, saturated fatty acids activate, and polyunsaturated omega-3s reduce, the innate immune response (via Toll-like receptors, as discussed in chapter 6). In addition, omega-6 and omega-3 fatty acids modulate another major driver of inflammation, the eicosanoid system (prostaglandins, thromboxanes, and leukotrienes). With brain composition and immune function being intimately linked to the body's lipid profile, it is not surprising that dietary lipids influence cognitive function and aging.

In general, a large body of studies, with a few exceptions, [244] [245] shows that saturated fat consumption is associated with increased cognitive decline/dementia, while omega-3 fatty acids are associated with reduced risks. This is discussed in greater detail below.

Saturated Fat and Cholesterol

Both human epidemiologic studies and controlled animal dietary experiments implicate saturated fat in impaired cognition and/or dementia. Many prospective dietary studies have shown that increased dietary saturated fat consumption increased the risk of dementia by as much as two or three fold.[246-255] One prospective study (Rotterdam) showed increased risk with saturated fat after two years of follow-up, though not after six years.[256] Animal studies also implicate saturated fat. For example, young rats fed a high-saturated-fat diet for three months showed impaired learning and memory relative to those fed low-fat chow. No impairment occurred with high poly- or mono-unsaturated-fat diets.[257]

Diets with high saturated- or trans-fat content adversely affect serum cholesterol,[258] increasing LDL and decreasing HDL.[259] [260] Several prospective epidemiologic studies have shown that elevated midlife serum cholesterol levels are a risk for Alzheimer's disease/cognitive decline.[261-262] One study of 444 Finnish men, for example,

found that elevated blood cholesterol in midlife was associated with a threefold increased risk of developing Alzheimer's disease in late life.[263] Studies looking at cholesterol levels in later life have generally not found an association with Alzheimer's disease/dementia risk.[264] This may be due to alterations in cholesterol metabolism and diet that occur early in the onset of dementia.[265-267]

Dietary and serum cholesterol may promote cognitive impairment by increasing amyloid-beta generation and deposition.[268-269] This is illustrated in a study in which a high-fat/high-cholesterol diet worsened Alzheimer's pathology, including amyloid-beta accumulation, in an Alzheimer's mouse model. Plasma and central nervous system total cholesterol were strongly correlated with amyloid-beta.[270]

Many prospective dietary studies have shown that increased dietary saturated fat consumption increased the risk of dementia by as much as two or three fold.

Omega-3 and Omega-6 Fatty Acids

Omega-3 and omega-6 fatty acids are both essential but their biological effects differ. Omega-3 fatty acids have anticlotting and anti-inflammatory properties.[271] Their essential role in infant brain development has been recognized for decades. Only more recently have their effects on brain aging been explored. In laboratory studies, omega-3s have been shown to benefit learning and memory in rodents. Remarkably, omega-3s have also been shown to have striking benefits in older rodents. For example, DHA (a long-chain omega-3 fatty acid) supplementation in aged rats improved memory-related learning, hippocampal fatty acid levels, and synaptic function, and reduced hippocampal oxidative markers.[272 273] Another study showed that administering DHA to aged Alzheimer's-prone rats reduced total amyloid-beta by more than 70 percent compared with low-DHA or control chow diets. Image analysis of brain sections showed plaque burden was reduced by more than 40 percent.[274]

A large body of human epidemiologic studies (11 of 13 prospective and 3 of 3 cross-sectional studies) indicate that dietary omega-3s and/or fish consumption (the major source of long-chain omega-3 fatty acids) substantially reduce the risk of Alzheimer's disease/cognitive decline.[275-289] For example, a recent Minneapolis study of over 2,200 men and women aged 50–60 years found that intake of long-chain omega-3s (DHA and EPA) was associated with less decline in verbal fluency (odds ratio 0.74). Subjects with hypertension and dyslipidemia showed greatest benefit, with the risk of verbal fluency decline reduced by about half (odds ratio approximately 0.5).[290] In addition, a double-blind, randomized, placebo-controlled clinical intervention study showed a mild positive effect of omega-3

Dietary omega-3s and/or fish consumption substantially reduce the risk of Alzheimer's disease/cognitive decline.

fatty acids on the rate of cognitive decline in patients with very mild Alzheimer's disease.[291]

Interestingly, a recent large prospective study[as] found that the use of omega-6 oils—that was not offset by use of omega-3-rich oils or fish—more than doubled the risk of dementia (hazard ratio 2.12). This effect was not seen among ApoE4 carriers.[292] Such an effect would be consistent with the role of omega-6 fatty acids as substrate for inflammatory mediators (eicosanoids) that are implicated in neuroinflammation. The potential for excessive omega-6 fatty acids to interfere in omega-3 fatty acid cognitive benefits is illustrated in an animal study showing that the reversal of learning impairments[at] in omega-3-deficient rats occurred only when omega-3s were restored to the diet and omega-6s were reduced. Restoring omega-3s alone (without reducing the high intake of omega-6 fatty acids) did not reverse the learning impairment.[293]

Fruits and Vegetables

Though relatively few human epidemiologic studies have been done, most indicate that high intake of fruits and vegetables is associated with decreased risks of cognitive decline.[294-300] This association is further supported by studies in animal models showing that fruit and vegetable extracts protect against cognitive and brain neuropathology from dietary oxidative stress in aged rodents.[301 302] The benefits of fruits and vegetables are thought to be due to various antioxidant and bioactive components including vitamins E and C, carotenoids, flavonoids, and other polyphenols.[303]

Antioxidants

Evidence from animal and laboratory studies shows that vitamin E and other antioxidant nutrients reduce oxidative and inflammatory damage.[304] Limited prospective studies on the effects of food intake of vitamin E and vitamin C in humans, however, are inconsistent. Studies on the effects of vitamin C and E supplements have generally been negative. For vitamin E, this may be due in part to the fact that vitamin E supplements have traditionally contained only one of at least eight naturally occurring forms of tocopherol.[305]

Polyphenols

Plant polyphenols are a large class of natural antioxidants suspected to be responsible for some of the health benefits of fruit and vegetable

[as] *The study followed over 8,000 French subjects for approximately 3.5 yrs.*
[at] *Learning was tested in a brightness-discrimination learning test.*

consumption. In addition to antioxidant characteristics, polyphenols also demonstrate a variety of neuroprotective properties in animal and in vitro studies. The polyphenol curcumin, which is contained in the spice turmeric, for example, has been shown to inhibit amyloid-beta aggregation and fibril formation in vitro. When fed to aged Alzheimer-prone mice with advanced amyloid accumulation,[au] curcumin reduced levels of amyloid and plaque burden.[306] Similarly, blueberry extracts, highly concentrated with acanthocyanin polyphenols, have been shown to prevent and even reverse age-related deficits in neuronal signaling and cognition in rats.[av 307 308] Blueberry supplementation was also shown to increase neurogenesis and improve memory performance in aged rats.[309] Polyphenols also act as free radical scavengers, regulate nitric oxide, inhibit cell proliferation, and reduce the immobilization of leukocytes.[310]

Studies ... indicate that high intake of fruits and vegetables is associated with decreased risks of cognitive decline.

Polyphenols can be subdivided into 10 or more classes based on chemical structure.[aw] Over 6,000 members of the flavonoid family alone have been identified,[311] including acanthocyanins, found in high concentrations in blueberries;[312] resveratrol, found in red wine; and catechins, in green tea and some cocoa and chocolate.

While the scarcity of studies does not yet permit conclusions to be drawn, limited laboratory, animal, and human epidemiologic evidence is highly suggestive that dietary polyphenols have a significant neuroprotective influence.

Very few epidemiologic studies have looked specifically at the possible influence of polyphenols in cognitive decline/Alzheimer's disease. Two studies in the French PAQUID cohort, with over 1,300 participants, did find consistent flavonoid associations with improved cognition.[313 314] Specifically, the studies found that flavonoid intake was associated with better cognitive function at baseline. At five years, the adjusted relative risk of dementia was approximately cut in half for subjects in the two highest tertiles of flavonoid intake compared to the lowest. And at 10 years follow-up, subjects in the lowest quartile of flavonoid intake had lost an average of 2.1 points on the Mini-Mental State Exam, compared with a loss of 1.2 points among those in the highest quartile of flavonoid intake.

A recent review of prospective cohort studies[315] found that 7 of 12 studies showed flavonoid intake associated with reduced risk of coronary artery disease. One study in Welsh men[316] found the opposite

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[au] *Tg2576 mice, (carrying a mutant form of amyloid precursor protein), were raised on a Purina chow diet with 500 ppm curcumin added, until the age of 22 months.*

[av] *Some, though not all, improvements were also demonstrated in rats receiving spinach and strawberry extracts, also high in polyphenols.*

[aw] *All plant poyphenols share the chemical structural feature of a central aromatic ring with one or more hydroxyl groups.*

In addition to antioxidant characteristics, polyphenols also demonstrate a variety of neuroprotective properties in animal and in vitro studies.

association, though the results did not achieve statistical significance (p=0.1) and may have been influenced by methodology problems.[ax]

Vitamins B6, B12, Folate, and Homocysteine

Homocysteine, an amino acid, is the byproduct of the metabolism of other amino acids (specifically the conversion of methionine to cysteine). While extreme elevations of homocysteine are caused by a rare genetic disorder (homocystinuria), mild-to-moderate elevations found in 5–7 percent of the population are most commonly caused by dietary deficiencies of folate, B12, and B6,[ay 317 318] vitamins that are essential for homocysteine metabolism. Moderate elevation of homocysteine is recognized as an independent risk factor for cardiovascular, cerebrovascular, and venous thromboembolic disease, (heart attacks, strokes and blood clots). The risks associated with homocysteine elevations, however, appear to be less than those associated with traditional cardiovascular risk factors.[319-321]

Lowering homocysteine through vitamin supplementation has not been shown to be of benefit for cardiovascular or venous thromboembolic disease.[322] Several large controlled clinical trials are now underway to assess the benefit of folate, B12, and B6 supplementation in preventing cardiovascular disease.

Evidence linking homocysteine elevations (and/or inadequate intake of folate, B12, and B6) to dementia/cognitive decline is mixed but increasingly suggestive. One recent large observational study of over a thousand older subjects found elevated plasma homocysteine a strong risk factor for the development of dementia and Alzheimer's disease.[323] Another large observational study found that higher dietary folate intake (which reduces homocysteine) was associated with reduced risk of developing Alzheimer's disease. Specifically, those in the highest quartile of folate intake showed half the risk of developing Alzheimer's disease (compared to lowest quartile).[324] These studies were notable for lasting 8 and 6 years. Two shorter observational studies—lasting 2.7 and 3.9 years—did not see an association between dietary folate/B12/B6 and incidence of Alzheimer's disease, perhaps because the observation time was too short to allow the effect to be seen.[325 326] Further support for an association of homocysteine levels with cognitive decline is provided by a recent large cross-sectional study showing higher plasma homocysteine

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[ax] *The result was thought potentially due to residual confounding, and/or possibly to the British habit of adding milk to tea, (the major source of flavonols in this population), inhibiting the absorption of flavonols.*

[ay] *Additional causes of mild-moderate homocysteine elevations include genetic defects, chronic medical conditions, pharmaceuticals, and other factors.*

levels are associated with silent brain infarcts and smaller brain volume on MRI in healthy, middle-aged adults.[az] [327]

Recently, clinical intervention studies have begun to test the influence of the relevant B vitamins (and the resulting homocysteine lowering) on cognitive function over time. Results of these early intervention studies—which have been limited by modest duration and sample sizes—have been mixed. [328-331] However, a recent trial with a larger subject number and longer duration [ba] found that folate supplementation was associated with a 26 percent reduction in plasma homocysteine and improved cognitive function[bb] compared to the placebo group.[332] Additional intervention studies will be needed to confirm this emerging role of homocysteine in cognitive decline and the role of folate supplementation in preventing this increased risk.

Rich food sources of folate include legumes (lentils, chick peas), green leafy vegetables (spinach, turnip greens, lettuces), sunflower seeds, and certain other fruits and vegetables. Some breakfast cereals are fortified with folic acid. The USDA provides a database of selected food sources of folate (and other nutrients) which can be found at the USDA National Nutrient Database for Standard Reference.

Dietary Patterns: The Mediterranean-Type Diet

As mentioned above, there is increasing interest in the influence of dietary patterns rather than single nutrients on a variety of health concerns. A focus on dietary patterns can capture complex interactions among many components that are difficult or impossible to see when looking at one or two nutrients individually.[333]

Interest in one such pattern, the Mediterranean diet, was first kindled by the work of Ancel Keys in the 1950s, who pointed out the very low rates of coronary disease and some cancers and long life expectancy on the island of Crete, despite high fat intake in the diet.[bc] While there is no single Mediterranean diet, the term is generally used to refer to diets characterized by high intake of vegetables, legumes, fruits, whole cereals, fish, nuts, and unsaturated fatty acids (especially olive oil); low-moderate dairy products; low saturated fats and meat; and regular moderate ethanol, primarily in the form

Interest in the Mediterranean diet was first kindled by the work of Ancel Keys in the 1950s, who pointed out the very low rates of coronary disease and some cancers and long life expectancy on the island of Crete, despite high fat intake in the diet.

[az] *The study included over 1900 subjects in the Framingham Offspring Study in a cross-sectional investigation.*

[ba] *Additional techniques included more sensitive outcome measures (testing specific cognitive domains rather than global performance), and statistical clustering of multiple raw test scores (to reduce variability of individual tests and improve the "robustness" of the measurements).*

[bb] *Improvements in cognitive function were found in memory, information processing speed, attention and concept shifting (similar to executive function), referred to by the author as sensorimotor speed.*

[bc] *It is now acknowledged that the benefits attributed to the Mediterranean diet in the Keys studies may have been influenced by poorly controlled co-variants such as physical activity.*

Adherence to the Mediterranean diet was associated with a risk of Alzheimer's disease that was reduced by more than a third.

of wine with meals. The benefits of the Mediterranean diet have generally been attributed to the combined effects of high content of antioxidants (in olive oil, vegetables, and fruits), high omega-3 fatty acids, low saturated fat,[334] low glycemic index, and high fiber content (due to reliance on whole rather than processed grains). We use the term Mediterranean-type diet here to refer to other diets as well, such as the "prudent" diet, that share most of the above characteristics.

The Lyon Heart Study was the first clinical trial showing compelling health benefits—specifically a 73 percent reduction in recurrent heart attacks and a 70 percent reduction in total mortality in a group of over 600 patients randomly assigned to a Mediterranean-type diet (vs. conventional medical dietary advice) following a heart attack.[335] Subsequently, a large body of observational and intervention studies (though not all studies) have shown benefits of a Mediterranean-type diet on the spectrum of diseases in the Western disease cluster. Beneficial effects have been shown for diabetes,[336] [337] obesity, metabolic syndrome,[338] chronic inflammation,[339] cardiovascular disease, and abnormal blood lipids.[340]

Several recent prospective studies have also demonstrated benefits of the Mediterranean diet in reducing cognitive decline[341] and Alzheimer's disease. One study following over 2,000 New York residents found that adherence to the Mediterranean diet over four years was associated with a risk of Alzheimer's disease that was reduced by more than a third.[bd] [342] Another prospective study of 192 community-living individuals with Alzheimer's disease found that those in the highest third for adherence to the Mediterranean diet had a markedly lower mortality risk (OR 0.27) as well as nearly four years longer survival, relative to those in the lowest third for adherence.[343]

Ethanol

Mild-to-moderate alcohol consumption has been recognized to have a protective effect against cardiovascular disease in middle-aged and older adults.[344] Similarly, a growing body of evidence suggests that light-to-moderate alcohol consumption is protective against dementia, [345] though high levels of alcohol intake and alcoholism itself are associated with cognitive dysfunction[346] and dementia. The alcohol-dementia association may also be complicated by other factors (including smoking, head trauma, and vitamin, antioxidant, and dietary deficiencies).[347]

Two large cohort studies showed substantial risk reduction for dementia (hazard ratio = 0.46-0.58) with light-to-moderate alcohol consumption.[348] [349] A study of over 11,000 US nurses also showed that consumption of one drink per day or less was associated with a

[bd] *OR= 0.6, comparing the most to least adherent thirds of the population*

reduced risk of cognitive impairment, (with relative risk compared with abstinence = 0.85).[350] A recent meta-analysis of 23 studies concluded that limited alcohol intake in earlier adult life may be protective against the development of dementia in later life. The relative risk for dementia and Alzheimer's disease was approximately 0.6.[351]

The ApoE4 gene appears to modify—and potentially even reverse—the alcohol benefit. Several (though not all[352]) observational studies suggest that individuals carrying the ApoE4 gene do not benefit from mild-to-moderate alcohol intake.[353 354] In a study of over 1,300 French subjects (59–71 years old) followed for four years, non-ApoE4 carriers who reported drinking two or more glasses of alcohol per day had a roughly 50 percent decrease in the risk of cognitive deterioration compared to nondrinkers. In contrast, those who carried at least one ApoE4 gene showed a positive association between alcohol consumption and cognitive deterioration.[355]

Two studies showed a reduced risk of dementia only with wine consumption[356 357] while others found no difference in risks according to beverage type.[358 359]

Mechanisms by which alcohol may exert protective effects are not clearly established, though the benefits of red wine consumption are thought to be due in part at least to the polyphenol resveratrol. Alcohol is also a modulator of fatty acid metabolism, specifically promoting higher levels of long-chain omega-3 fatty acids,[360 361] which are associated with reduced risk for cognitive decline/Alzheimer's disease. It has been speculated that a "fish-like effect of moderate wine drinking" might partly explain the protective effects of wine drinking against cardiovascular disease.[362] If so, it is possible that such an effect might play a role in the neuroprotective effect of limited alcohol consumption.

A growing body of epidemiological evidence suggests an association between occupational exposure to extremely low frequency magnetic fields and dementia/ Alzheimer's disease.

Electromagnetic Field Exposure

A growing body of epidemiological evidence suggests an association between occupational exposure to extremely low frequency magnetic fields (ELF-MF) and dementia/Alzheimer's disease. ELF-MF are generated by electric-powered equipment,[be] among other sources. They are part of a spectrum of electromagnetic waves that run from gamma rays at the highest frequency end, through x-rays, ultraviolet rays, visible light, infrared radiation, microwaves, radio waves, very low frequency, and extremely low frequency waves at the lowest end. Most research has focused on long-term health effects in workers exposed to magnetic fields typically encountered by electric power installers and repairers, power plant operators, electricians, electrical and electronic

[be] *Power-frequency fields are typically 50–60 Hz.*

equipment repairers, telephone line technicians, seamstresses, tailors, welders, carpenters, or others who operate electrical equipment.[363] [364]

A recent systematic review and meta-analysis[365] found a 1.6 to twofold increased risk[bf] for those occupationally exposed to electromagnetic fields, using 14 published epidemiologic studies with adequate methodology.[bg] Another review prepared for the BioInitiative Working Group found six out of seven epidemiologic studies[bh] generally positive for an association between ELF-MF and Alzheimer's disease, with only one study failing to find an association.[366]

...this evidence is suggestive that extremely low frequency magnetic fields could potentially increase risk for Alzheimer's disease by reducing brain levels of neuroprotective melatonin.

One of the mechanisms proposed to mediate the increased risk of Alzheimer's disease with ELF-MF exposure is reduced melatonin production. Numerous epidemiologic studies (11 of 13 reviewed in the BioInitiative Working Group study) found that high ELF-MF exposure was associated with reduced melatonin production in occupational and residential settings. [367] Melatonin has been shown to be neuroprotective in a number of animal and in vitro studies. Melatonin effects include inhibition of amyloid beta neurotoxicity, oxidative stress in transgenic mouse models of Alzheimer's disease, and proinflammatory cytokine production induced by amyloid-beta in rat brains.

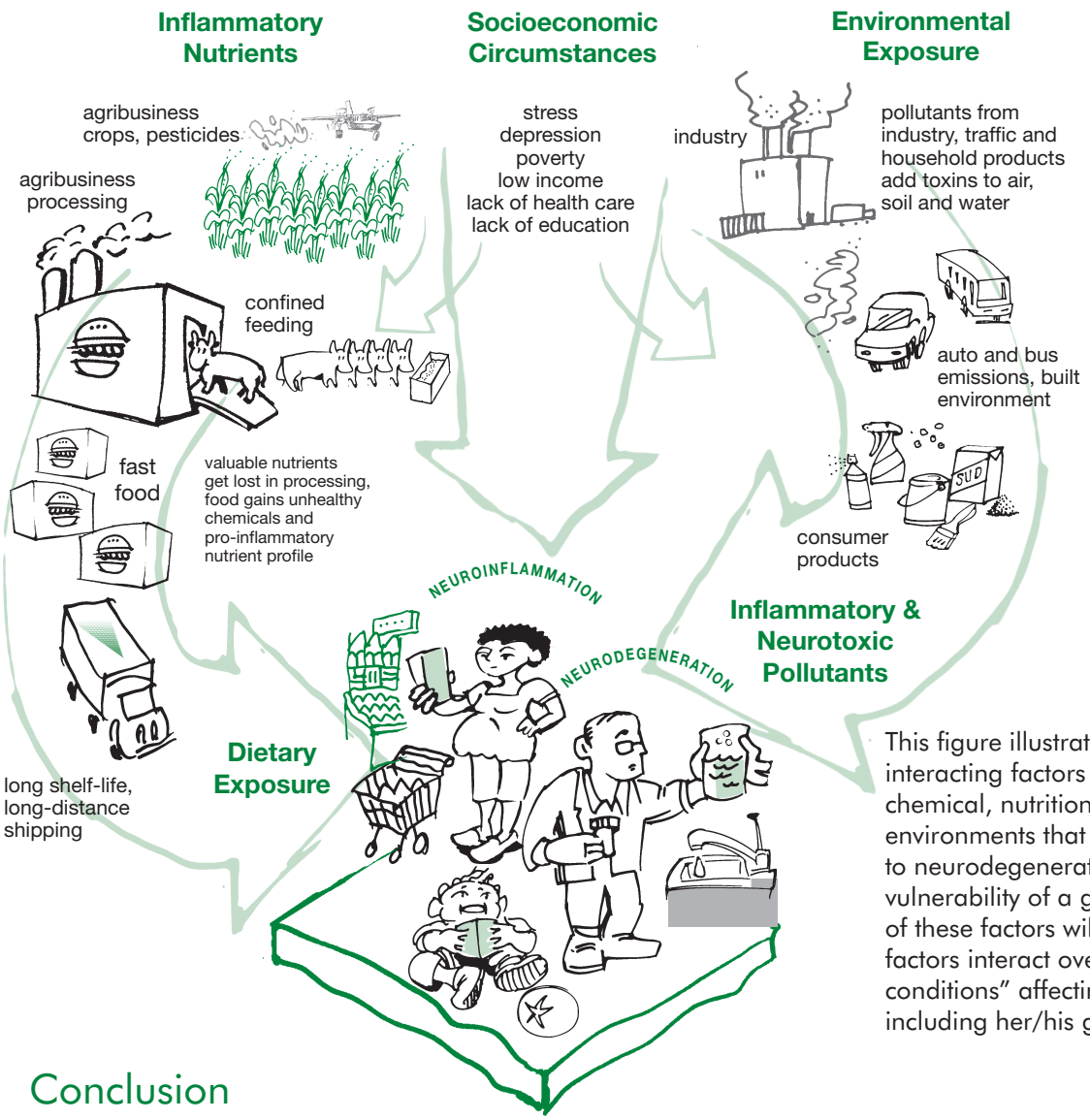
Studies in humans show that although melatonin levels normally decline with age, the levels are more sharply reduced in people with Alzheimer's disease, even in the earliest stages.[368] [369] One therapeutic trial in people with Alzheimer's disease concluded that melatonin supplements can stabilize cognitive decline.[370] Another study in people with Alzheimer's disease in group homes showed that, although melatonin improved sleep patterns, its effects on cognitive function were beneficial only when combined with bright lights during the day.[371] Melatonin supplementation also improved memory and learning in rat models of Alzheimer's disease.[372] Taken together, the evidence is suggestive that ELF-MF could potentially increase risk for Alzheimer's disease by reducing brain levels of neuroprotective melatonin. Human studies have not yet been designed to study this hypothesis.

Other mechanisms proposed to explain potential ELF-MF effects on the brain and biological systems in general include oxidative stress, calcium ion release in immune cells and neurons, apoptosis and necrosis in brain cells, and effects on biomagnetic particles in the brain.[373]

[bf] *The 1.6-fold increased risk was derived from cohort studies. The twofold increased risk was derived from case-control studies.*

[bg] *All included studies used standardized criteria for Alzheimer's diagnosis, and most studies used quantitative estimates of EMF exposure.*

[bh] *Criteria for this study required expert diagnoses and restrictive classification of magnetic field exposure.*



This figure illustrates some of the interacting factors in the modern chemical, nutritional, social and built environments that may be contributing to neurodegenerative disease. The vulnerability of a given individual to any of these factors will depend on how these factors interact over time in the "sea of conditions" affecting the individual – including her/his genetic make-up.

Conclusion

We have reviewed a number of environmental factors that substantially influence the risks of Alzheimer's/dementia and cognitive decline. These include elements of the chemical, nutritional, and social environment, as well as exercise and disease states—which are themselves responsive to many of these same influences. We turn now to examine the role of environmental influences in Parkinson's disease. Subsequently, we will discuss opportunities in policy innovations (in chapter 9) and personal actions to address these influences and reduce the risks for neurodegenerative disease and related Western disease cluster illnesses.

Endnotes

1 Bennett DA, Schneider JA, Arvanitakis Z, et al. Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology. 2006 Jun 27;66(12):1837-44.

2 Qiu C, De Ronchi D, Fratiglioni L. The epidemiology of the dementias: an update. Curr Opin Psychiatry. 2007;20:380-385.

3 Blass DM, Rabins PV. In the Clinic: Dementia. Annals of Internal Medicine. 2008;ITC4:1-16.

4 Wolfe M. Shutting down Alzheimer's. Scientific American. 2006;294(5):72-79.

5 Chafekar SM, Baas F, Scheper W. Oligomer-specific Abeta toxicity in cell models is mediated by selective uptake. Biochim Biophys Acta. 2008;1782(9):523-31.

6 Resende R, Ferreiro E, Pereira C, et al. Neurotoxic effect of oligomeric and fibrillar species of amyloid-beta peptide 1-42: Involvement of endoplasmic reticulum calcium release in oligomer-induced cell death. Neuroscience. 2008;155(3):725-37.

7 Wolfe M. Shutting down Alzheimer's. Scientific American. 2006;294(5):72-79.

8 Zigman W, Lott I. Alzheimer's disease in Down syndrome: neurobiology and risk. Ment Retard Dev Disabil Res Rev. 2007;13(3):2287-2293.

9 Leverenz J, Raskind M. Early amyloid deposition in the medial temporal lobe of young Down syndrome patients: a regional quantitative analysis. Exp Neurol. 1998;150:296–304.

10 Lott I, Head E, Doran E, et al. Beta-amyloid, oxidative stress, and down syndrome. Curr Alzheimer Res. 2006;3(5):521-528.

11 Nunomura A, Perry G, Pappolla M, et al. Neuronal oxidative stress precedes amyloid-beta deposition in Down syndrome. J Neuropathol Exp Neurol. 2000;59:1011–1017.

12 Tansley G, Burgess B, Bryan M, et al. The cholesterol transporter ABCG1 modulates the subcellular distribution and proteolytic processing of beta-amyloid precursor protein. J Lipid Res. 2007;48(5):1022-1034.

13 Lott I, Head E, Doran Busciglio J. Beta-amyloid, oxidative stress, and down syndrome. Curr Alzheimer 2006;3(5):521-528.

14 Nunomura A, Perry G, Pappolla M, et al. Neuronal oxidative stress precedes amyloid-beta deposition in Down syndrome. J Neuropathol Exp Neurol 2000;59:1011–1017.

15 Munoz DG, Feldman H. Causes of Alzheimer's disease. CMAJ. 2000;162(1):65-72.

16 Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA. 1997 Oct 22-29;278(16):1349-56.

17 Raber J, Huang Y, Ashford JW. ApoE genotype accounts for the vast majority of AD risk and pathology. Neurobiol Aging. 2004 May-Jun;25(5):641-50.

18 Haan MN, Shemanski L, Jagust WJ, et al. The role of APOE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. JAMA. 1999 Jul 7;282(1):40-6.

19 Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Disease Meta Analysis Consortium. JAMA. 1997 Oct 22-29;278(16):1349-56.

20 Corbo RM, Scacchi R. Apolipoprotein E allele distribution in the world. Is APOE4 a "thrifty" allele? Ann. Hum. Genet. 1999;63:301-310.

21 Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA. 1997 Oct 22-29;278(16):1349-56.

22 Tyas SL, Salazar JC, Snowdon DA, et al. Transitions to mild cognitive impairments, dementia, and death: findings from the Nun Study. Am J Epidemiol. 2007 Jun 1;165(11):1231-8.

23 Sawyer K, Sachs-Ericsson N, Preacher KJ, et al. Racial Differences in the Influence of the APOE Epsilon 4 Allele on Cognitive Decline in a Sample of Community-Dwelling Older Adults. Gerontology. 2008 Jun 5. [Epub ahead of print]

24 Ordovas JM, Mooser V. The APOE locus and the pharmacogenetics of lipid response. Curr Opin Lipidol. 2002 Apr;13(2):113-7.

25 Song Y, Stampfer MJ, Liu S. Meta-analysis: apolipoprotein E genotypes and risk for coronary heart disease. Ann Intern Med. 2004 Jul 20;141(2):137-47.

26 Martins IJ, Hone E, Foster JK, et al. Apolipoprotein E, cholesterol metabolism, diabetes, and the convergence of risk factors for Alzheimer's disease and cardiovascular disease. Mol Psychiatry. 2006 Aug;11(8):721-36.

27 Corbo RM, Scacchi R. Apolipoprotein E (APOE) allele distribution in the world. Is APOE*4 a 'thrifty' allele? Ann Hum Genet. 1999 Jul;63(Pt 4):301-10.

28 Wilson PW, Schaefer EJ, Larson MG, et al. Apolipoprotein E alleles and risk of coronary disease. A meta-analysis. Arterioscler Thromb Vasc Biol. 1996 Oct;16(10):1250-5.

29 Lane RM, Farlow MR. Lipid homeostasis and apolipoprotein E in the development and progression of Alzheimer's disease. J Lipid Res. 2005 May;46(5):949-68.

30 Dosunmu R, Wu J, Basha MR, et al. Environmental and dietary risk factors in Alzheimer's disease. Expert Rev. Neurotherapeutics. 2007;7(7):887-900.

31 Kivipelto M, Rovio S, Ngandu T, et al. Apolipoprotein E epsilon4 magnifies lifestyle risks for dementia: a population based study. J Cell Mol Med. 2008 Mar 4. [Epub ahead of print]

32 Hendrie HC, Ogunniyi A, Hall KS, et al. Incidence of dementia and Alzheimer disease in 2 communities: Yoruba residing in Ibadan, Nigeria, and African Americans residing in Indianapolis, Indiana. JAMA. 2001 Feb 14;285(6):739-47.

33 Gureje O, Ogunniyi A, Baiyewu O, et al. APOE epsilon4 is not associated with Alzheimer's disease in elderly Nigerians. Ann Neurol. 2006 Jan;59(1):182-5.

34 Murrell JR, Price B, Lane KA, et al. Association of apolipoprotein E genotype and Alzheimer disease in African Americans. Arch Neurol. 2006 Mar;63(3):431-4.

35 Ogunniyi A, Baiyewu O, Gureje O, et al. Epidemiology of dementia in Nigeria: results from the Indianapolis-Ibadan study. Eur J Neurol. 2000 Sep;7(5):485-90.

36 Osuntokun BO, Sahota A, Ogunniyi AO, et al. Lack of an association between apolipoprotein E epsilon 4 and Alzheimer's disease in elderly Nigerians. Ann Neurol. 1995 Sep;38(3):463-5.

37 Sahota A, Yang M, Gao S, et al. Apolipoprotein E-associated risk for disease in the African-American population is genotype dependent. Neurol. 1997 Oct;42(4):659-61.

38 Yang Y, Ruiz-Narvaez E, Kraft P, et al. Effect of apolipoprotein genotype and saturated fat intake on plasma lipids and myocardial infarction in the Central Valley of Costa Rica. Hum Biol. 2007 Dec;79(6):637-47.

39 Haan MN, Shemanski L, Jagust WJ, et al. The role of APOE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. JAMA. 1999 Jul 7;282(1):40-6.

40 Blair CK, Folsom AR, Knopman DS, et al. Atherosclerosis Risk in Communities (ARIC) Study Investigators. APOE genotype and cognitive decline in a middle-aged cohort. Neurology. 2005 Jan 25;64(2):268-76.

41 Stewart W, Schwartz B, Simon D, et al. ApoE genotype, past adult lead exposure, and neurobehavioral function. Environ Health Perspect. 2002;110(5):501-505.

42 Schmechel DE, Browndyke J, Ghio A. Strategies for dissecting genetic-environmental interactions in neurodegenerative disorders. Neurotoxicology. 2006;27(5):637-657.

43 Shih RA, Hu H, Weisskopf MG, et al. Cumulative lead dose and cognitive function in adults: a review of studies that measured both blood lead and bone lead. Environ Health Perspect. 2007 Mar;115(3):483-92.

44 Weisskopf MG, Wright RO, Schwartz J, et al. Cumulative lead exposure and prospective change in cognition among elderly men. Am J Epidemiology. 2004;160(12):1184-93.

45 Shih RA, Glass TA, Bandeen-Roche K, et al. Environmental lead exposure and cognitive function in community-dwelling older adults. Neurology 2006;67:1556-62.

46 Weisskopf MG, Proctor SP, Wright RO, et al. Cumulative lead exposure and cognitive performance among elderly men. Epidemiology. 2007;18:59-66.

47 Stewart W, Schwartz B, Simon D, et al. ApoE Genotype, Past Adult Lead Exposure, and Neurobehavioral Function. Environ Health Perspect. 2002;110(5).

48 Weisskopf MG, Wright RO, Schwartz J, et al. Cumulative lead exposure and cognitive performance among elderly men. Epidemiology 2007;18:59-66.

49 Basha MR, Murali M, Siddiqi HK, et al. Lead exposure and its effect on APP proteolysis and AB aggregation. FASEB J. 2005;19:2083-4.

50 Weisskopf MG, Proctor SP, Wright RO, et al. Cumulative lead exposure and cognitive performance among elderly men. Epidemiology 2007;18:59-66.

51 Stewart W, Schwartz B, Simon D, et al. ApoE Genotype, Past Adult Lead Exposure, and Neurobehavioral Function. Environ Health Perspect. 2002;110(5).

52 Ibid.

53 Wu J, Basha MR, Brock B, et al. Alzheimer's disease (AD)-like pathology in aged monkeys after infantile exposure to environmental metal lead (Pb): evidence for a developmental origin and environmental link for AD. J Neurosci. 2008;28(1):3-9.

54 Basha MR, Wei W, Bakheet SA, et al. The fetal basis of amyloidogenesis: exposure to lead and latent overexpression of amyloid precursor protein and beta-amyloid in the aging brain. J Neurosci. 2005;25(4):823-829.

55 Lahiri DK, Maloney B, Basha MR et al. How and when environmental agents and dietary factors affect the course of Alzheimer's disease: the LEARn model (latent early-life associated regulation) may explain the triggering of AD. Current Alzheimer Research. 2007;4:219-228.

56 Walton JR. Human range dietary aluminum equivalents cause cognitive deterioration in aged rats. Presented at the 24th International Neurotoxicology Conference. November, 2007. San Antonio, Texas.

57 Walton JR. A longitudinal study of rats chronically exposed to aluminum at human dietary levels. Neurosci Lett. 2007;412:29-33.

58 Walton JR. Human range dietary aluminum equivalents cause cognitive deterioration in aged rats. Presented at the 24th International Neurotoxicology Conference. November, 2007. San Antonio, Texas. Currently in preparation for publication.

59 Greger JL. Aluminum metabolism. Annu. Rev. Nutr. 1993;12:43-63.

60 Walton JR. longitudinal study of rats chronically exposed to aluminum at human dietary levels. Neurosci Lett. 2007;412:29-33.

61 Saiyed SM, Yokel RA. Aluminium content of some foods and food products in the USA, with aluminium food additives. Food Addit Contam. 2005 Mar;22(3):234-44.

62 Walton JR. Human range dietary aluminum equivalents cause cognitive deterioration in aged rats. Presented at the 24th International Neurotoxicology Conference. November, 2007. San Antonio, Texas. Currently in preparation for publication.

63 Walton JR. An aluminum-based rat model for Alzheimer's disease exhibits oxidative damage, inhibition of PP2A activity, hyperphosphorylated tau, and granulovacuolar degeneration. J Inorg Biochem 2007;101(9):1275-84.

64 Iqbal K, Grundke-Iqbal I. Alzheimer neurofibrillary degeneration: significance, etiopathogenesis, therapeutics and prevention. J Cell Mol Med. 2008 Jan-Feb;12(1):38-55.

65 Lukiw WJ, Percy ME, Kruck TP. Nanomolar aluminum induces pro-inflammatory and pro-apoptotic gene expression in human brain cells in primary culture. J Inorg Biochem. 2005;99(9):1895-1898.

66 European Food Safety Authority. Safety of aluminium from dietary intake. EFSA Journal. 2008;754:2-4.

67 Greger JL. Aluminum metabolism. Annu Rev Nutr. 1993;13:43-63.

68 Berthon, Guy. Aluminium speciation in relation to aluminum bioavailability, metabolism and toxicity. Coord Chem Rev. 2002;228:319-341.

69 Scientific opinion of the panel of food additives, flavourings, processing aids and food contact materials. The safety of aluminum from dietary intake. EFSA Journal. 2008;754:1-43. p. 29.

70 Byrne J. EFSA sets new intake for aluminium in food. Breaking News on Supplements & Nutrition – Europe July 16,2008. http://www.foodproductiondaily.com/Quality-Safety/EFSA-sets-new-intake-level-for-aluminium-in-food Accessed July 20, 2008.

71 ATSDR. Toxicologic Profile for Aluminum. Draft for Public Comment. Sept. 2006. http://www.atsdr.cdc.gov/toxprofiles/tp22.html Accessed 8/17/08.

72 Pratico D. Alzheimer's disease and oxygen radicals: new insights. Biochem Pharmacol. 2002;63:563-567.

73 Dosunmu R, Wu J, Basha MR, et al. Environmental and dietary risk factors in Alzheimer's disease. Expert Rev. Neurotherapeutics. 2007;7(7):887-900.

74 Silvestri L, Camaschella C. A potential pathogenetic role of iron in Alzeimer's Disease. J Cell Mol Med. 2008 May 1.

75 Lau FC, Shukitt-Hale B, Joseph JA. Nutritional intervention in brain aging: reducing the effects of inflammation and oxidative stress. Subcell Biochem. 2007;42:299-318.

76 Cole GM, Lim GP, Yang F, et al. Prevention of Alzheimer's disease: Omega-3 fatty acid and phenolic anti-oxidant interventions. Neurobiol Aging. 2005;26 Suppl 1:133-136.

77 Brook RD. Air Pollution. What is bad for the arteries might be bad for the veins. Arch Int Med. 2008;168(9):909-911.

78 Ibid.

79 Ibid.

80 Ibid.

81 Baccarelli A, Martinelli I, Zanobetti A, et al. Exposure to particulate air pollution and risk of deep vein thrombosis. Arch Intern Med. 2008 May 12;168(9):920-7.

82 Brook RD. Air Pollution. What is bad for the arteries might be bad for the veins. Arch Int Med. 2008;168(9):909-911.

83 Calderón-Garcidueñas L, Reed W, Maronpot RR, et al. Brain Inflammation and Alzheimer's-like pathology in individuals exposed to severe air pollution. Toxicol Pathol. 2004;32:650-658.

84 Calderón-Garcidueñas L, Solt AC, Henríquez-Roldán C, et al. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults.Toxicol Pathol. 2008;36(2):289-310.

85 Calderón-Garcidueñas L, Reed W, Maronpot RR, et al. Brain Inflammation and Alzheimer's-like pathology in individuals exposed to severe air pollution. Toxicol Pathol. 2004;32:650-658.

86 Calderón-Garcidueñas L, Solt AC, Henríquez-Roldán C, et al. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults.Toxicol Pathol. 2008;36(2):289-310.

87 Calderón-Garcidueñas L., Franco-Lira M, Torres-Jardon R, et al. Pediatric respiratory and systemic effects of chronic air pollution exposure: nose, lung, heart, and brain pathology. Toxicol Pathol. 2007;35:154-162.

88 Rao DB, Wong BA, McManus BE, et al. Inhaled iron, unlike manganese, is not transported to the rat brain via the olfactory pathway. Toxicol Appl Pharmacol. 2003 Nov 15;193(1):116-26.

89 Tjälve H, Henriksson J. Uptake of metals in the brain via olfactory pathways. Neurotoxicology. 1999 Apr-Jun;20(2-3):181-95.

90 Oberdörster G, Sharp Z, Atudorei V, et al. Translocation of inhaled ultrafine particles to the brain. Inhal Toxicol. 2004 Jun;16(6-7):437-45.

91 Calderón-Garcidueñas L., Franco-Lira M, Torres-Jardon R, et al. Pediatric respiratory and systemic effects of chronic air pollution exposure: nose, lung, heart, and brain pathology. Toxicol Pathol. 2007;35:154-162.

92 Calderón-Garcidueñas L, Reed W, Maronpot RR, et al. Brain Inflammation and Alzheimer's-like pathology in individuals exposed to severe air pollution. Toxicol Pathol. 2004;32:650-658.

93 Calderón-Garcidueñas L, Solt AC, Henríquez-Roldán C, et al. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. Toxicol Pathol. 2008;36(2):289-310.

94 Ibid.

95 Calderón-Garcidueñas L, Mora-Tiscareño A, Ontiveros E, et al. Air pollution, cognitive deficits and brain abnormalities: pilot study with children and dogs. Brain Cogn. 2008 Jun 10. [ahead of print]

96 Campbell A, Oldham M, Becaria A, et al. Particulate matter in polluted air may increase biomarkers of inflammation in mouse brain. Neurotoxicology. 2005;26(1):133-40.

97 Mohankumar SM, Campbell A, Block M, et al. Particulate matter, oxidative stress and neurotoxicity.Neurotoxicology. 2008 May;29(3):478-87.

98 Hartz AM, Bauer B., Block ML, et al. Diesel exhaust particles induce oxidative stress, proinflammatory signaling, and P-glycoprotein up-regulation at the blood-brain barrier. FASEB J. 2008 Aug;22(8):2723-33

99 Mohankumar SM, Campbell A, Block M, et al. Particulate matter, oxidative stress and neurotoxicity. Neurotoxicology. 2008 May;29(3):478-87.

100 Calderón-Garcidueñas L, Reed W, Maronpot RR, et al. Brain Inflammation and Alzheimer's-like pathology in individuals exposed to severe air pollution. Toxicol Pathol. 2004;32:650-658.

101 Hoshino T, Nakaya T, Homan T, et al. Involvement of prostaglandin E2 in production of amyloid-beta peptides both in vitro and in vivo. J Biol Chem. 2007 Nov 9;282(45):32676-88.

102 Kotilinek LA, Westerman MA, Wang Q, et al. Cyclooxygenase-2 inhibition improves amyloid-beta-mediated suppression of memory and synaptic plasticity. Brain. 2008 Mar;131(Pt 3):651-64.

103 Schantz S, Widholm J, Rice D. Effects of PCB exposure on neuropsychological function in children. Environ Health Perspect. 2003 111(3):357-576.

104 Lin K, Guo N, Tsai P, et al. Neurocognitive changes among elderly exposed to PCBs/PCDFs in Taiwan. Environ Health Perspect. 2008;116:184-189.

105 Schantz SL, Gasior DM, Polverejan E, et al. Impairments of memory and learning in older adults exposed to polychlorinated biphenyls via consumption of Great Lakes fish. Environ Health Perspect. 2001;108:605-611.

106 Steenland K, Hein MJ, Cassinelli RT, et al. Polychlorinated biphenyls and neurodegenerative disease mortality in an occupational cohert. Epidemiology. 2006;17(1):8-13.

107 Mele PC, Bowman RE, Levin ED. Behavioral evaluation of perinatal PCB exposure in rhesus monkeys: fixed-interval performance and reinforcement-omission. Neurobehav Toxicol Teratol. 1986;8:131–138.

108 Schantz SL, Levin ED, Bowman Heironimus MP, et al. Effects of perinatal PCB exposure on discrimination-reversal learning in monkeys. Neurotoxicol Teratol. 1989;11:243–250.

109 Seegal RF, Bush B, Brosch KO. Comparison of effects of Aroclors 1016 and 1260 on non-human primate catecholamine function. Toxicology. 1991;66:145–163.

110 Lee DH, Lee IK, Song K. A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National and Examination Survey 1999-2002. Diabetes Care. 2006 Jul;29(7):1638-44.

111 Lee DH, Lee IK, Jin SH, et al. Association between serum concentrations of persistent organic pollutants and insulin resistance among nondiabetic adults: results from the National and Nutrition Examination Survey 1999-2002. Diabetes Care. 2007 Mar;30(3):622-8.

112 Lee DH, Lee IK, Porta M, et al. Relationship between serum concentrations of persistent organic pollutants and the prevalence of metabolic syndrome among non-diabetic adults: results from the National and Nutrition Examination Survey 1999-2002. Diabetologia. 2007 Sep;50(9):1841-51.

113 Ha MH, Lee DH, Jacobs DR. Association between serum concentrations of persistent organic pollutants and self-reported cardiovascular disease prevalence: results from the National Health and Nutrition Survey, 1999-2002. Environ Perspect. 2007 Aug;115(8):1204-9.

114 Arsenescu V, Arsenescu RI, King V, et al. Pcb-77 induces adipocyte differentiation and proinflammatory adipokines and promotes obesity and atherosclerosis. Environ Health Perspect. 2008;116(6):761-768.

115 Song MO, Freedman JH. Activation of mitogen activated protein kinases by PCB126 (3,3',4,4',5-pentachlorobiphenyl) in HepG2 cells. Toxicol Sci. 2005 Apr;84(2):308-18.

116 Ibid.

117 Hennig B, Hammock BD, Slim R, et al. PCB-induced oxidative stress in endothelial cells: modulation by nutrients. Int J Hyg Health. 2002 Mar;205(1-2):95-102.

118 Matsusue K Ishii Y, Ariyoshi N, et al. A highly toxic coplanar polychlorinated biphenyl compound suppresses delta 5 and delta 6 desaturates activities which play key roles in arachidonic acid synthesis in rat liver. Chem. Rev Toxicol. 1999;12:1158-65.

119 Alzoubi KH, Gerges NZ, Aleisa AM, et al. Levothyroxin restores hypothyroidism-induced impairment of hippocampus-dependent learning and memory: Behavioral, electrophysiological, and molecular studies. Hippocampus. 2008 Aug 4. [Epub ahead of print]

120 Hogervorst E, Huppert F, Matthews FE, et al. Thyroid function and cognitive decline in the MRC Cognitive Function and Aging Study. Psychoneuroendocrinology. 2008 Aug;33(7):1013-22.

121 Kamel F, Hoppin JA. Association of pesticide exposure with neurologic dysfunction and disease. Environ Health Perspect. 2004 Jun;112(9):950-8.

122 Kamel F, Engel LS, Gladen BC, et al. Neurologic symptoms in licensed pesticide applicators in the Agricultural Health Study. Hum Exp Toxicol. 2007 Mar;26(3):243-50.

123 Baldi I, Filleul L, Mohammed-Brahim B, et al. Neuropsychologic effects of long-term exposure to pesticides: results from the French phytoner study. Environ Health Perspect. 2001;109:839-844.

124 Kamel F, Hoppin JA. Association of pesticide exposure with neurologic dysfunction and disease. Environ Health Perspect. 2004 Jun;112(9):950-8.

125 Baldi I Filleul L, Mohammed-Brahim B, et al. Neuropsychologic effects of long-term exposure to pesticides: results from the French phytoner study. Environ Health Perspect. 2001;109:839-844.

126 Rosenstock L, Keifer M, Daniell WE, et al Chronic central nervous system effects of acute organophosphate pesticide intoxication. The Pesticide Effects Study Group. Lancet. 1991 Jul 27;338(8761):223-7.

127 Steenland K, Dick RB, Howell RJ, et al. Neurologic function among termiticide applicators exposed to chlorpyrifos. Environ Health Perspect. 2000 Apr;108(4):293-300.

128 Savage EP, Keefe TJ, Mounce LM, et al. Chronic neurological sequelae of acute organophosphate pesticide poisoning. Arch Environ Health. 1988 Jan-Feb;43(1):38-45.

129 Kamel F, Hoppin JA. Association of pesticide exposure with neurologic dysfunction and disease. 2004 Jun;112(9):950-8.

130 Daniell W, Barnhart S, Demers P, et al. Neuropsychological performance among agricultural pesticide applicators. Environ Res. 1992 Oct;59(1):217-28.

131 Ames RG, Steenland K, Jenkins B, et al. Chronic neurologic sequelae to cholinesterase inhibition among agricultural pesticide applicators. Arch Environ Health. 1995 Nov-Dec;50(6):440-4.

132 Kamel F, Hoppin JA. Association of pesticide exposure with neurologic dysfunction and disease. Environ Health Perspect. 2004 Jun;112(9):950-8.

133 Baldi I et al. Neuropsychologic effects of long-term exposure to pesticides: results from the French phytoner study. Environ Health Perspect. 2001;109:839-844.

134 Cole DC et al. Neurobehavioral outcomes among farm and nonfarm rural Ecuadorians. Neurotoxicology and Teratology. 1997;19:277-286.

135 Baldi I, Filleul L, Mohammed-Brahim B, et al. Neuropsychologic effects of long-term exposure to pesticides: results from the French phytoner study. Environ Health Perspect. 2001;109:839-844.

136 The Canadian Study of and Aging: risk factors for Alzheimer's disease in Canada. Neurology. 1994 Nov;44(11):2073-80.

137 Baldi I, Lebailly P, Mohammed-Brahim B, et al. Neurodegenerative diseases and exposure to pesticides in the elderly. Am Journal of Epidemiology 2003;157(5):409-414.

138 Tyas SL, Manfreda J, Strain LA, et al. Risk factors for Alzheimer's disease: a population-based, longitudinal study in Manitoba, Canada. Int J Epidemiol. 2001;30(3):590-7.

139 Gun RT, Korten AE, Jorm AF, et al. Occupational risk factors for Alzheimer disease: a case-control study. Alzheimer Dis Assoc Disord. 1997 Mar;11(1):21-7.

140 Lindsay J, Laurin D, Verreault R, et al. Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. Am J Epidemiol. 2002 Sep 1;156(5):445-53.

141 Bosma H, van Boxtel M, Ponds R, et al. Pesticide exposure and risk of mild cognitive dysfunction. Lancet. 2000;356:912-3.

142 Gauthier E, Fortier I, Courchesne F, et al. Environmental pesticide exposure as a risk factor for Alzheimer's disease: a case-control study. Environ Res. 2001;86:37-45.

143 Kivipelto M, Ngandu T, Fratiglioni L, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol. 2005;62:1556-1560.

144 Biessels GJ, Staekenborg S, Brunner E, et al. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol. 2006 Jan;5(1):64-74.

145 Shadlen MF, Larson EB. Risk factors for dementia. UpToDate online medical reference text. Uptodate.com Referenced 6/27/08.

146 Yaffe K, Blackwell T, Kanaya AM, et al. Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. Neurology. 2004;63:658-663.

147 van Oijen M, Okereke OI, Kang JH, et al. Fasting insulin levels and cognitive decline in older women without diabetes. Neuroepidemiology. 2008;30:174-9.

148 Okereke OI, Pollack MN, Hu FB, et al. Plasma C-peptide levels and rates of cognitive decline in older, community-dwelling women without diabetes. Psychoneuroendocrinology. 2008;33(4)455-61, 2008.

149 Irie F, Fitzpatrick A, Lopez O, et al. Enhanced risk for Alzheimer disease in persons with type 2 diabetes and apoE4. Arch Neurol. 2008;65:89-93.

150 Lovestone S. Diabetes and dementia: is the brain another site of end-organ damage? Neurology. 1999;53:1907.

151 Irie F, Fitzpatrick A, Lopez O, et al. Enhanced risk for disease in persons with type 2 diabetes and apoE4. Arch Neurol. 2008;65:89-93.

152 Peila R, Rodriguez B, Launer L. Type 2 diabetes, apoE gene, and the risk for dementia and related pathologies: the Honolulu-Asia aging study. Diabetes. 2002;51:1256-1262.

153 Gustafson D. Adiposity indices and dementia. Lancet Neurol. 2006 Aug;5(8):713-20.

154 Kivipelto M, Ngandu T, Fratiglioni L, et al. Obesity and vascular risk factors at midlife and the risk of dementia and disease. Arch Neurol. 2005;62:1556-1560.

155 Gustafson DR, Rothenberg E, Blennow K, et al. An 18-year follow up of overweight and risk for Alzheimer's disease. Arch Intern Med. 2003;163:1524–28.

156 Rosengren A, Skoog I, Gustafson D, et al. Body mass index, other cardiovascular risk factors, and hospitalization for dementia. Arch Intern Med. 2005;165:321–26.

157 Luchsinger JA, Patel B, Tang MX, et al. Measures of adiposity and dementia risk in elderly persons. Arch Neurol. 2007 Mar;64(3):392-8.

158 Whitmer RA, Gunderson EP, Barrett-Connor E, et al. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. BMJ. 2005 Jun 11;330(7504):1360.

159 Nourhashemi F, Deschamps V, Larrieu S, et al. Body mass index and incidence of dementia: the PAQUID study. Neurology. 2003; 60:117–19.

160 Stewart R, Masaki K, Xue QL, et al. A 32-year prospective study of change in body weight and incident dementia: the Honolulu-Asia Aging Study. Arch Neurol. 2005; 62:55–60.

161 Whitmer RA, Gunderson EP, Barrett-Connor E, et al. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. BMJ. 2005 Jun 11;330(7504):1360.

162 Elias MF, Elias PK, Sullivan LM, et al. Obesity, diabetes and cognitive deficit: the Framingham Heart Study. Neurobiol Aging. 2005; 26 Suppl 1:11-6.

163 Waldstein SR, Katzel LI. Interactive relations of central versus total obesity and blood pressure to cognitive function. Int J Obes (Lond) 2006; 30: 201–17.

164 Cournot M, Marquié JC, Ansiau D, et al. Relation between body mass index and cognitive function in healthy middle-aged men and women. Neurology. 2006 Oct 10;67(7):1208-14.

165 Waldstein SR, Katzel LI. Interactive relations of central versus total obesity and blood pressure to cognitive function. Int J Obes (Lond). 2006;30:201–17.

166 Jagust W, Harvey D, Mungas D, et al. Central obesity and the aging brain. Arch Neurol. 2005 Oct;62(10):1545-8.

167 Ward MA, Carlsson CM, Trivedi MA, et al. The effect of body mass index on global brain volume in middle-aged adults: a cross sectional study. BMC Neurol. 2005 Dec 2;5:23.

168 Jagust W, Harvey D, Mungas D, et al. Central obesity and the aging brain. Arch Neurol. 2005 Oct;62(10):1545-8.

169 Brickman AM, Schupf N, Manly JJ, et al. Brain morphology in older African Americans, Caribbean Hispanics, and Whites from northern Manhattan. Neurol. 2008 Aug;65(8):1053-61.

170 Gustafson D, Lissner L, Bengtsson C, et al. A 24-year follow-up of body mass index and cerebral atrophy. Neurology. 2004 Nov 23;63(10):1876-81. Summary for patients in: Neurology. 2004 Nov 23;63(10):E19-20.

171 Gazdzinski S, Kornak J, Weiner MW, et al. Body mass index and magnetic resonance markers of brain integrity in adults. Ann Neurol. 2008 May;63(5):652-7.

172 Razay, G, Vreugdenhil, A, Wilcock, G. The metabolic syndrome and Alzheimer disease. Arch Intern Med. 2007;64:93-6.

173 Kalmijn S, Foley D, White L, et al. Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men. The Honolulu-Asia aging study. Arterioscler Thromb Vasc Biol. 2000;20:2255-60.

174 Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA. 2004; 292:2237-42.

175 Yaffe K, Haan M, Blackwell T, et al. Metabolic syndrome and cognitive decline in elderly Latinos: findings from the Sacramento Area Latino Study of Aging study. J Am Geriatr Soc. 2007 May;55(5):758-62.

176 Muller M, Tang MX, Schupf N, et al. Metabolic syndrome and dementia risk in a multiethnic elderly cohort. Dement Geriatr Cogn Disord. 2007;24:185-92.

177 Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA. 2004; 292:2237.

178 Rafnsson SB, Deary IJ, Smith FB, et al. Cognitive decline and markers of inflammation and hemostasis: the Edinburgh artery study. J Am Geriatr Soc. 2007;55:700.

179 Schram MT, Euser SM, de Craen AK, et al. Systemic markers of inflammation and cognitive decline in old age. J Am Geriatr Soc. 2007;55:708-16.

180 Tan ZS, Beiser AS, Vasan RS, et al. Inflammatory markers and the risk of Alzheimer disease: the Framingham Study. Neurology. 2007;68:1902-8.

181 Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA. 2004; 292:2237-42.

182 Yaffe K, Haan M, Blackwell T, et al. Metabolic syndrome and cognitive decline in elderly Latinos: findings from the Sacramento Area Latino Study of Aging study. J Am Geriatr Soc. 2007 May;55(5):758-62.

183 Dik MG, Jonker C, Hack CE, et al. Serum inflammatory proteins and cognitive decline in older persons. Neurology. 2005 26;64(8):1371-7.

184 Engelhart MJ, Geerlings MI, Meijer J, et al. Inflammatory proteins in plasma and the risk of dementia: the Rotterdam study. Arch Neurol. 2004 May;61(5):668-72.

185 Yaffe K, Lindquist K, Penninx BW, et al. Inflammatory markers and cognition in well-functioning African-American and white elders. Neurology. 2003 Jul 8;61(1):76-80.

186 Schmidt R, Schmidt H, Curb JD, et al. Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia Aging Study. Ann Neurol. 2002 Aug;52(2):168-74.

187 Weaver JD, Huang MH, Albert M, et al. Interleukin-6 and risk of cognitive decline: MacArthur studies of successful aging. Neurology. 2002 Aug 13;59(3):371-8.

188 Weuve J, Ridker PM, Cook NR, et al. High-sensitivity C-reactive protein and cognitive function in older women. Epidemiology. 2006 Mar;17(2):183-9.

189 Holovoet P, Lee DH, Steffes M, et al. Association between circulating oxidized Low-density lipoprotein and incidence of the metabolic syndrome. JAMA. 2008;299:2287-2293.

190 Albert MS. Changing the trajectory of cognitive decline? N Engl J Med. 2007;357(5):502-3.

191 Fischer A, Sananbenesi Fm Wang X, et al. Recovery of learning and memory is associated with chromatin remodeling. Nature. 2007;447:178-82.

192 Van Praag H, et al. Neural consequences of environmental enrichment. Nat Rev Neurosci. 2000;1:191-8.

193 Shadlen MF et al. Risk factors for dementia. UpToDate online medical reference text. Uptodate.com Referenced 6/27/08.

194 Fratiglioni L, Palliard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. Lancet Neurol. 2004;3(6):343-53.

195 Barnes LL, Mendes de Leon CF, Wilson RS, et al. Social resources and cognitive decline in a population of older African Americans and whites. Neurology. 2004;63(12):2322-6.

196 Rovio S, Kareholt I, Viitanen B, et al. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. Lancet Neurol. 2005;4(11):705-11.

197 Wilson RS, Scherr PA, Schneider JA, et al. Relation of cognitive activity to risk of developing Alzheimer disease. Neurology. 2007;69(20):1911-20,

198 Flynn MG, McFarlin BK, Phillips MD, et al. Toll-like receptor 4 and CD14 mRNA expression are lower in resistive exercise-trained elderly women. J Appl Physiol. 2003 Nov;95(5):1833-42.

199 Brooks SV, Vasilaki A, Larkin LM, et al. Repeated bouts of aerobic exercise lead to reductions in skeletal muscle free radical generation and nuclear factor kappaB activation. J Physiol. 2008;586(16):3979-90.

200 Attipoe S, Park JY, Fenty N, et al. Oxidative stress levels are reduced in postmenopausal women with exercise training regardless of hormone replacement therapy status. J Women Aging. 2008;20(1-2):31-45.

201 Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation. 1999 Apr 27;99(16):2192-217.

202 Geerlings MI, Schmand B, Braam AW, et al. Depressive symptoms and risk of Alzheimer's disease in more highly educated older people. J Am Geriatr Soc. 2000 Sep;48(9):1092-7.

203 Ownby RL, Crocco E, Acevedo A, et al. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry. 2006;63:530–538.

204 Chen P, Ganguli M, Mulsant BH, et al. The temporal relationship between depressive symptoms and dementia: a community-based prospective study. Arch Gen Psychiatry. 1999;56:261–266.

205 Ganguli M, Du Y, Dodge HH, et al. Depressive symptoms and cognitive decline in late life: a prospective epidemiological study. Arch Gen Psychiatry. 2006;63:153–160.

206 Ownby RL, Crocco E, Acevedo A, et al. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry. 2006;63:530–538.

207 Wilson RS, Evans DA, Bienias JL, et al. Proneness to psychological distress is associated with risk of Alzheimer's disease. Neurology. 2003 Dec 9;61(11):1479-85.

208 Wilson RS, Arnold SE, Schneider JA, et al. Chronic psychological distress and risk of Alzheimer's disease in old age. Neuroepidemiology. 2006;27(3):143-53.

209 Videbech P, Ravnkilde B. Hippocampal volume and depression: a meta-analysis of MRI studies. Am J Psychiatry. 2004;161:1957–1966

210 Campbell S, Marriott M, Nahmias C, et al. Lower hippocampal volume in patients suffering from depression: a meta-analysis. Am J Psychiatry. 2004;161:598–607.

211 Geerlings MI, Schmand B, Braam AW, et al. Depressive symptoms and risk of Alzheimer's disease in more highly educated older people. J Am Geriatr Soc. 2000 Sep;48(9):1092-7.

212 Stress System Malfunction Could Lead to Serious, Life Threatening Disease. NIHBackgrounder. http://www.nih.gov/news/pr/sep2002/nichd-09.htm . Accessed 8/08.

213 Johnson JD, O'Connor KA, Deak T, et al. Prior stressor exposure primes the HPA axis. Psychoneuroendocrinology. 2002 Apr;27(3):353-65.

214 Parker KJ, Schatzberg AF, Lyons DM. Neuroendocrine aspects of hypercortisolism in major depression. Horm Behav. 2003;43:60–66.

215 Magri F, Cravello L, Barili L, et al. Stress and dementia: the role of the hypothalamicpituitary-adrenal axis. Aging Clin Exp Res. 2006 18(2):167-70.

216 Sapolsky RM, Uno H, Rebert CS, et al. Hippocampal damage associated with prolonged glucocorticoid exposure in primates. J Neurosci. 1990;10:2897–2902.

217 Lupien SJ, Schwartz G, Ng YK, et al. The Douglas Hospital Longitudinal Study of Normal and Pathological Aging: summary of findings. J Psychiatry Neurosci. 2005 Sep;30(5):328-34.

218 Magri F, Cravello L, Barili L, et al. Stress and dementia: the role of the hypothalamicpituitary-adrenal axis. Aging Clin Exp Res. 2006 Apr;18(2):167-70.

219 Wilson RS, Evans DA, Bienias JL, et al. Proneness to psychological distress is associated with risk of Alzheimer's disease. Neurology. 2003 Dec 9;61(11):1479-85.

220 Kang JE, Cirrito JR, Dong H, et al. Acute stress increases interstitial fluid amyloid-beta via corticotropin-releasing factor and neuronal activity. Proc Natl Acad Sci U S A. 2007 Jun 19;104(25):10673-8.

221 Dong H, Goico B, Martin M, et al. Modulation of hippocampal cell proliferation, memory, and amyloid plaque deposition in APPsw (Tg2576) mutant mice by isolation stress. Neuroscience. 2004;127(3):601-9.

222 Ross R. Atherosclerosis—an inflammatory disease. N Eng J Med. 1999;340:115-126.

223 Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation. 1999 Apr 27;99(16):2192-217.

224 Suarez EC, Krishnan RR, Lewis JG. The relation of severity of depressive symptoms to monocyte-associated proinflammatory cytokines and chemokines in apparently healthy men. Psychosom Med. 2003 May-Jun;65(3):362-8.

225 Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, et al. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. Proc Natl Acad Sci U S A. 2003 Jul 22;100(15):9090-5.

226 Kiecolt-Glaser JK, Belury MA, Porter K, et al. Depressive symptoms, omega-6:omega-3 fatty acids, and inflammation in older adults. Psychosom Med. 2007 Apr;69(3):217-24.

227 Maes M, Christophe A, Bosmans E, et al. In humans, serum polyunsaturated fatty acid levels predict the response of proinflammatory cytokines to psychologic stress. Biol Psychiatry. 2000 May 15;47(10):910-20.

228 Johnson JD, O'Connor KA, Deak T, et al. Prior stressor exposure sensitizes LPS-induced cytokine production. Brain Behav Immun. 2002 Aug;16(4):461-76.

229 Bierhaus A, Wolf J, Andrassy M, et al. A mechanism converting psychosocial stress into mononuclear cell activation. Proc Natl Acad Sci U S A. 2003 Feb 18;100(4):1920-5.

230 Blumenthal JA, Sherwood A, Babyak MA, et al. Effects of exercise and stress management training on markers of cardiovascular risk in patients with ischemic heart disease: a randomized controlled trial. JAMA. 2005 Apr 6;293(13):1626-34.

231 Tofler GH. Psychosocial factors in coronary and cerebral vascular disease. UpToDate on line medical text. www.uptodate.com. Accessed 7/30/2008.

232 Frasure-Smith N, Lespérance F, Prince RH, et al. Randomised trial of home-based psychosocial nursing intervention for patients recovering from myocardial infarction. Lancet. 1997 Aug 16;350(9076):473-9.

233 Jones DA, West RR. Psychological rehabilitation after myocardial infarction: multicentre randomised controlled trial. BMJ. 1996 Dec 14;313(7071):1517-21.

234 Ngandu T, von Strauss E, Helkala et al. Education and dementia: what lies behind the association? Neurology 2007;69(14):1442-1450.

235 Fratiglioni L, Winblad B, von Strauss E. Prevention of disease and dementia. Major findings from the Kungsholmen Project. Physiol Behav. 2007;92(1-2):98-104

236 Fotenos A, Mintun M, Snyder A, et al. Brain volume decline in aging: evidence for a relation between socioeconomic status, preclinical Alzheimer disease, and reserve. Arch Neurol. 2008;65(1):113-120.

237 Stampfer MJ, Hu FB, Manson JE, et al. Primary prevention of coronary heart disease in women through diet and lifestyle. N Engl J Med. 2000 Jul 6;343(1):16-22.

238 De Logeril M, Salen P, Martin JL, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon diet heart study. Circulation 1999;99:797-785.

239 Parrott MD, Greenwood CE. Dietary influences on cognitive function with aging. Ann NY Acad Sci. 2007;114:389-397.

240 Dosunmu R, Wu J, Basha MR, et al. Environmental and dietary risk factors in Alzheimer's disease. Expert Rev. Neurotherapeutics. 2007;7(7):887-900.

241 Morris, MC. Diet and Disease: what the evidence shows. MedGenMed, 6(1): 1-5, 2004.

242 Ibid.

243 Barberger-Gateau P, Raffaitin C, Letenneur L, et al. Dietary patterns and risk of dementia: the Three-City cohort study. Neurology. 2007 Nov 13;69(20):1921-30.

244 Engelhart MJ, Geerlings MI, Ruitenberg A, et al. Diet and risk of dementia: Does fat matter?: The Rotterdam Study. Neurology. 2002 Dec 24;59(12):1915-21.

245 Laurin D, Verreault R, Lindsay J, et al. Omega-3 fatty acids and risk of cognitive impairment and dementia. J Alzheimers Dis. 2003 Aug;5(4):315-22.

246 Morris MC, Evans DA, Bienias JL, et al. Dietary fats and the risk of incident Alzheimer disease. Arch Neurol. 2003 Feb;60(2):194-200. Erratum in: Neurol. 2003 Aug;60(8):1072.

247 Luchsinger JA, Tang MX, Shea S, et al. Caloric intake and the risk of Alzheimer disease. Arch Neurol. 2002 Aug;59(8):1258-63.

248 Kalmijn S, Launer LJ, Ott A, et al. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. Ann Neurol. 1997 Nov;42(5):776-82.

249 Engelhart MJ, Geerlings MI, Ruitenberg et al. Diet and risk of dementia: Does fat matter?: The Rotterdam Study. Neurology. 2002 Dec 24;59(12):1915-21.

250 Beydoun MA, Kaufman JS, Satia JA, et al. Plasma n-3 fatty acids and the risk of cognitive decline in older adults: the Atherosclerosis Risk in Communities Study. Am J Clin Nutr. 2007 85(4):1103-11.

251 Kalmijn S, van Boxtel MP, Ocké M, et al. Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. Neurology. 2004 Jan 27;62(2):275-80.

252 Heude B, Ducimetière P, Berr C; EVAStudy. Cognitive decline and fatty acid composition of erythrocyte membranes--The Study. J Clin Nutr. 2003 Apr;77(4):803-8.

253 Tully AM, Roche HM, Doyle R, et al. Low serum cholesteryl ester-docosahexaenoic acid levels in disease: a case-control study. Br J Nutr. 2003 89(4):483-9.

254 Laitinen MH, Ngandu T, Rovio S, et al. Fat intake at midlife and risk of dementia and disease: a population-based study. Dement Geriatr Cogn Disord. 2006;22(1):99-107.

255 Morris MC, Evans DA, Bienias JL, et al. Dietary fat intake and 6-year cognitive change in an older biracial community population. Neurology. 2004 May 11;62(9):1573-9.

256 Morris MC. Diet and Alzheimer's disease: what the evidence shows. MedGenMed. 2004 Jan 15;6(1):48.

257 Greenwood CE, Winocur G. Cognitive impairment in rats fed high-fat diets: a specific effect of saturated fatty-acid intake. Behav Neurosci. 1996 Jun;110(3):451-9.

258 Gillman M. Dietary Fat. In UpToDate online medical textbook. Accessed 6/30/08.

259 Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipids and lipoproteins. meta-analysis of 27 trials. Arterioscler Thromb. 1992 Aug;12(8):911-9.

260 Mensink RP, Katan MB. of dietary trans fatty acids on high-density and low-density lipoprotein cholesterol levels in healthy subjects. N Engl J Med. 1990 Aug 16;323(7):439-45.

261 Solomon A, Kåreholt I, Ngandu T, et al. Serum cholesterol changes after midlife and late-life cognition: twenty-one-year follow-up study. Neurology. 2007 Mar 6;68(10):751-6.

262 Whitmer RA, Sidney S, Selby J, et al. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology. 2005 Jan 25;64(2):277-81.

263 Notkola IL, Sulkava R, Pekkanen J,et al. Serum total cholesterol, apolipoprotein Eepsilon 4 allele, and Alzheimer's disease. Neuroepidemiology. 1998;17(1):14-20.

264 Reitz C, Luchsinger J, Tang MX, et al. Impact of plasma lipids and time on memory performance in healthy elderly without dementia. Neurology. 2005 Apr 26;64(8):1378-83

265 Shadlen M, Larson E. Risk factors for dementia. In UpToDate online medical textbook. www.uptodate.com. Accessed 6/27/08.

266 Mielke, MM, Zandi, PP, Sjogren, M, et al. High total cholesterol levels in late life associated with a reduced risk of dementia. Neurology 2005; 64:1689.

267 Solomon A, Kareholt, I, Ngandu, T, et al. Serum cholesterol changes after midlife and late-life cognition: twenty-one-year follow-up study. Neurology 2007; 68:751.

268 Puglielli L, Tanzi RE, Kovacs DM. Alzheimer's disease: the cholesterol connection. Nat Neurosci. 2003 Apr;6(4):345-51.

269 Dosunmu R, Wu J, Basha MR, et al. Environmental and dietary risk factors in Alzheimer's disease. Expert Rev. Neurotherapeutics. 2007;7(7):887-900.

270 Refolo LM, Malester B, LaFrancois J, et al. Hypercholesterolemia accelerates the amyloid pathology in a transgenic mouse model. Neurobiol Dis. 2000 Aug;7(4):321-31. Erratum in: Neurobiol Dis 2000 Dec;7(6 Pt B):690.

271 Morris MC. Diet and Alzheimer's disease: what the evidence shows. MedGenMed. 2004 Jan 15;6(1):48.

272 McGahon BM, Martin DS, Horrobin DF, et al. Age-related changes in synaptic function: analysis of the effect of dietary supplementation with omega-3 fatty acids. Neurobiol Aging. 1999;94(1):305-14.

273 Gamoh S, Hashimoto M, Hossain S, et al. Chronic administration of docosahexaenoic acid improves the performance of radial arm maze task in aged rats. Clin Exp Pharmacol Physiol. 2001 Apr;28(4):266-70.

274 Lim GP, Calon F, Morihara T, et al.. diet enriched with the omega-3 fatty acid docosahexaenoic acid reduces amyloid burden in an aged Alzheimer mouse model. J Neurosci. 2005 Mar 23;25(12):3032-40.

275 van Gelder BM, Tijhuis M, Kalmijn S, et al. Fish consumption, n-3 fatty acids, and subsequent 5-y cognitive decline in elderly men: the Zutphen Elderly Study. Am J Clin Nutr. 2007 Apr;85(4):1142-7.

276 Freund-Levi Y, Basun H, Cederholm T, et al. Omega-3 supplementation in mild to moderate Alzheimer's disease: effects on neuropsychiatric symptoms. Int J Geriatr Psychiatry. 2008 Feb;23(2):161-9

277 Freund-Levi Y, Eriksdotter-Jönhagen M, Cederholm T, et al. Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD study: a randomized double-blind trial. Arch Neurol. 2006 Oct;63(10):1402-8

278 Schaefer EJ, Bongard V, Beiser AS, et al. Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham Heart Study. Arch Neurol. 2006 Nov;63(11):1545-50.

279 Morris MC, Evans DA, Tangney CC, et al. Fish consumption and cognitive decline with age in a large community study. Arch Neurol. 2005 Dec;62(12):1849-53.

280 Kalmijn S, van Boxtel MP, Ocké M, et al. Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. Neurology. 2004 Jan 27;62(2):275-80.

281 Heude B, Ducimetière P, Berr C; EVAStudy. Cognitive decline and fatty acid composition of erythrocyte membranes--The Study. J Clin Nutr. 2003 Apr;77(4):803-8.

282 Morris MC, Evans DA, Bienias JL, et al. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. Arch Neurol. 2003 Jul;60(7):940-6.

283 Tully AM, Roche HM, Doyle R, et al. Low serum cholesteryl ester-docosahexaenoic acid levels in Alzheimer's disease: a case-control study. Br J Nutr. 2003 89(4):483-9.

284 Laurin D, Verreault R, Lindsay J, et al. Omega-3 fatty acids and risk of cognitive impairment and dementia. J Alzheimers Dis. 2003 Aug;5(4):315-22.

285 Engelhart MJ, Geerlings MI, Ruitenberg A, et al. Diet and risk of dementia: Does fat matter?: The Rotterdam Study. Neurology. 2002 Dec 24;59(12):1915-21.

286 Barberger-Gateau P, Letenneur L, Deschamps V, et al. Fish, meat, and risk of dementia: cohort study. BMJ. 2002 Oct 26;325(7370):932-3.

287 Conquer JA, Tierney MC, Zecevic J et al, Fatty acid analysis of blood plasma of patients with disease, other types of dementia, and cognitive impairment. Lipids. 2000 Dec;35(12):1305-12.

288 Kalmijn S, Launer LJ, Ott A,et al. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. Ann Neurol. 1997 Nov;42(5):776-82.

289 Kalmijn S, Feskens EJ, Launer LJ, et al. Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. Am J Epidemiol. 1997 Jan 1;145(1):33-41.

290 Beydoun MA, Kaufman JS, Satia JA, et al. Plasma n-3 fatty acids and the risk of cognitive decline in older adults: the Atherosclerosis Risk in Communities Study. J Clin Nutr. 2007 Apr;85(4):1103-11.

291 Freund-Levi Y, Eriksdotter-Jönhagen M, Cederholm T, et al. Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD study: a randomized double-blind trial. Arch Neurol. 2006 Oct;63(10):1402-8

292 Barberger-Gateau P, Raffaitin C, Letenneur L, et al. Dietary patterns and risk of dementia: the Three-City cohort study. Neurology. 2007 Nov 13;69(20):1921-30.

293 Ikemoto A, Ohishi M, Sato Y, et al. Reversibility of n-3 fatty acid deficiency-induced alterations of learning behavior in the rat: level of n-6 fatty acids as another critical factor. J Lipid Res. 2001 Oct;42(10):1655-63.

294 Barberger-Gateau P, Raffaitin C, Letenneur L, et al. Dietary patterns and risk of dementia: the Three-City cohort study. Neurology. 2007 Nov 13;69(20):1921-30.

295 Dai Q, Borenstein AR, Wu Y, et al. Fruit and vegetable juices and Alzheimer's disease: the Kame Project. J Med. 2006; 119:751.

296 Morris, MC, Evans, DA, Tangney, CC, et al. Associations of vegetable and fruit consumption with age-related cognitive change. Neurology. 2006;67:1370-6.

297 Kang JH, Ascherio A, Grodstein F. Fruit and vegetable consumption and cognitive decline in aging women. Ann Neurol. 2005; 57:713-20.

298 Ortega RM, Requejo AM, Andres, et al. Dietary intake and cognitive function in a group of elderly people. Am J Clin Nutr. 1997;66:803-9.

299 Lee L, Kang SA, Lee HO, et al. Relationships between dietary intake and cognitive function level in Korean elderly people. Public Health. 2001;115:133-8.

300 Press D, Alexander M. Prevention of dementia. In UpToDate. www.uptodate.com, accessed 6/30/08.

301 Morris MC, DA, Tagney CC, et al. Associations of vegetable and fruit consumption with age-related cognitive change. Neurology. 2006; 67:1370-6.

302 Chan A, Shea TB. Supplementation with apple juice attenuates presenilin-1 overexpression during dietary and genetically-induced oxidative stress. J Dis. 2006 Dec;10(4):353-8.

303 Morris MC, Evans DA, Tangney CC, et al. Associations of vegetable and fruit consumption with age-related cognitive change. Neurology. 2006; 67:1370-6.

304 Morris MC. Diet and Alzheimer's disease: what the evidence shows. MedGenMed. 2004 Jan 15;6(1):48.

305 Ibid.

306 Yang F, Lim GP, Begum AN, et al. Curcumin inhibits formation of amyloid-beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo. J Biol Chem. 2005 Feb 18;280(7):5892-901.

307 Joseph JA, Shukitt-Hale B, Denisova NA, et al. Reversals of age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits with blueberry, spinach, or strawberry dietary supplementation. J Neurosci. 1999 Sep 15;19(18):8114-21.

308 Youdim KA, Shukitt-B, Martin A, et al. Short-term dietary supplementation of blueberry polyphenolics: beneficial effects on aging brain performance and peripheral tissue function. Nutr Neurosci. 2000;3:383-97.

309 Casadesus G, Shukitt-Hale B, Stellwagen HM, et al. Modulation of hippocampal plasticity and cognitive behavior by short-term blueberry supplementation in aged rats. Nutr Neurosci. 2004 Oct-Dec;7(5-6):309-16.

310 Arts IC, Hollman PC. Polyphenols and disease risk in epidemiologic studies. Am J Clin Nutr. 2005 Jan;81(1 Suppl):317S-325S. Review.

311 Ibid.

312 Lau FC, Shukitt-Hale B, Joseph JA. Nutritional intervention in brain aging: reducing the effects of inflammation and oxidative stress. Subcell Biochem. 2007;42:299-318. Review.

313 Letenneur L, Proust-Lima C, Le Gouge A, et al. Flavonoid intake and cognitive decline over a 10-year period. Am J Epidemiol. 2007 Jun 15;165(12):1364-71.

314 Commenges D, Scotet V, Renaud S, et al. Intake of flavonoids and risk of dementia. Eur J Epidemiol. 2000 Apr;16(4):357-63.

315 Arts IC, Hollman PC. Polyphenols and disease risk in epidemiologic studies. Am J Clin Nutr. 2005 Jan;81(1 Suppl):317S-325S.

316 Hertog MG, Sweetnam PM, Fehily AM, et al. Antioxidant flavonols and ischemic heart disease in a Welsh population of men: the Caerphilly Study. Am J Clin Nutr. 1997 May;65(5):1489-94.

317 Rosenson RS, Dang DS. Overview of homocysteine in UpToDate online medical text. www.uptodate.com, accessed 6/30/08.

318 Selhub J. Homocysteine metabolism. Annu Rev Nutr.1999;19:217-46.

319 Dang DS. Overview of homocysteine in UpToDate online medical text. www.uptodate.com, accessed 6/30/08.

320 Shadlen M, Larson E. Risk factors for dementia. In UpToDate online medical textbook. www.uptodate.com. Accessed 6/27/08.

321 Clarke R. Homocysteine, B vitamins, and the risk of dementia. Am J Clin Nutr. 2007;85:329-30.

322 Bonaa KH, Njolstad I, Ueland PM, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med 2006; 354:1578-88.

323 Seshadri S et al. Plasma homocysteine as a risk factor for dementia and alzheimer's disease. N Eng J Med. 2002;346:476-83.

324 Luchsinger JA, Tang MX, Miller J, et al. Relation of higher folate intake to lower risk of Alzheimer disease in the elderly. Arch Neurol. 2007;64:86-92.

325 Kalmijn S, Launer LJ, Lindemans J, et al. Total homocysteine and cognitive decline in a community-based sample of elderly subjects: the Rotterdam Study. Am J Epidemiol. 1999 Aug 1;150(3):283-9.

326 Morris MC, Evans DA, Schneider JA, et al. Dietary folate and vitamins B-12 and B-6 not associated with incident Alzheimer's disease. J Alzheimers Dis. 2006 9(4):435-43.

327 Seshadri S, Wolf PA, Beiser AS, et al. Association of plasma total homocysteine levels with subclinical brain injury: cerebral volumes, white matter hyperintensity, and silent brain infarcts at volumetric magnetic resonance imaging in the Framingham Offspring Study. Arch Neurol. 2008 May;65(5):642-9.

328 Durga J, van Boxtel MP, Schouten EG, et al. Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. Lancet. 2007;369:208.

329 Press D, Alexander M. Prevention of dementia. In UpToDate. www.uptodate.com, accessed 6/30/08.

330 McMahon JA, Green TJ, Skeaff CM, et al. A controlled trial of homocysteine lowering and cognitive performance. N Engl J Med. 2006;354:2764-72.

331 Shadlen M, Larson E. Risk factors for dementia. In UpToDate online medical textboot. www.uptodate.com. Accessed 6/27/08.

332 Durga J, van Boxtel MP, Schouten EG, et al. Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. Lancet. 2007;369:208-16.

333 Hu FB. The Mediterranean diet and mortality – olive oil and beyond. N Engl J Med 2003. 348;26:2595-6.

334 Ibid.

335 de Lorgeril M, Salen P, Martin JL, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation. 1999 Feb 16;99(6):779-85.

336 van Dam RM, Rimm EB, Willett WC, et al. Dietary patterns and risk for type 2 diabetes mellitus in U.S. men. Ann Intern Med. 2002 Feb 5;136(3):201-9.

337 Panagiotakos DB, Tzima N, Pitsavos C, et al. The association between adherence to the Mediterranean diet and fasting indices of glucose homoeostasis: the ATTICAStudy. J Am Coll Nutr. 2007 Feb;26(1):32-8.

338 Esposito K, Marfella R, Ciotola M, et al. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA. 2004 Sep 22;292(12):1440-6.

339 Giugliano D, K. Mediterranean diet and metabolic diseases. Curr Opin Lipidol. 2008 Feb;19(1):63-8.

340 Estruch R, Martínez-González MA, Corella D, et al. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. Ann Intern Med. 2006 Jul 4;145(1):1-11.

341 Panza F, Solfrizzi V, Colacicco AM, et al. Mediterranean diet and cognitive decline. Public Health Nutr. 2004 Oct;7(7):959-63.

342 Scarmeas N, Stern Y, Tang MX, et al. Mediterranean diet and risk for Alzheimer's disease. Annal Neurol. 2006 Jun;59(6):912-21.

343 Scarmeas N, Luchsinger JA, Mayeux R, et al. Mediterranean diet and Alzheimer disease mortality. Neurology. 2007 Sep 11;69(11):1084-93.

344 Tolstrup J, Grønbaek M. Alcohol and atherosclerosis: recent insights. Curr Atheroscler Rep. 2007 Aug;9(2):116-24.

345 Shadlen M, Larson E. Risk factors for dementia. In UpToDate online medical textbook. www.uptodate.com. Accessed 6/27/08.

346 Thomas VS, Rockwood KJ. Alcohol abuse, cognitive impairment and mortality among older people. J Am Geriatr Soc. 2001;49:415-20.

347 Haan MN, Wallace R. Can dementia be prevented? Brain aging in a population-based context. Annu Rev Public Health. 2004,25:1-24.

348 Mukamal KJ, Kuller HL, Fitzpatrick AL, et al. Prospective study of alcohol consumption and risk of dementia in older adults. JAMA. 2003;289:1405-1413.

349 Haan MN, Wallace R. Can dementia be prevented? Brain aging in a population-based context. Annu Rev Public Health. 2004,25:1-24.

350 Evans DA, Bienias JL. Alcohol consumption and cognition. N Eng J Med. 2005;352:3:289-90.

351 Peters R, J, Warner J, Beckett N, et al. Alcohol, dementia and cognitive decline in the elderly: a systematic review. Age Ageing. 2008;37(5):505-12.

352 Stampfer MJ, Kang JH, Chen J, et al. Effects of moderate alcohol consumption on cognitive function in women. N Engl J Med. 2005 Jan 20;352(3):245-53.

353 Dufouil C, Tzourio C, Brayne C, et al. Influence of apolipoprotein Egenotype on the risk of cognitive deterioration in moderate drinkers and smokers. Epidemiology. 2000 May;11(3):280-4.

354 Luchsinger JA, Tang MX, Siddiqui M, et al. Alcohol intake and risk of dementia. J Am Geriatr Soc. 2004 Apr;52(4):540-6.

355 Dufouil C, Tzourio C, Brayne C, et al. Influence of apolipoprotein Egenotype on the risk of cognitive deterioration in moderate drinkers and smokers. Epidemiology. 2000 May;11(3):280-4.

356 Truelsen T, Thudium D, Grønbaek M; Copenhagen City Heart Study. Amount and type of alcohol and risk of dementia: the Copenhagen City Study. Neurology. 2002 Nov 12;59(9):1313-9.

357 Luchsinger JA, Tang MX, Siddiqui M, et al. Alcohol intake and risk of dementia. J Am Geriatr Soc. 2004 52(4):540-6.

358 Stampfer MJ, Kang JH, Chen J, et al. Effects of moderate alcohol consumption on cognitive function in women. N Engl J Med. 2005 Jan 20;352(3):245-53.

359 Mukamal KJ, Kuller HL, Fitzpatrick AL, et al. Prospective study of alcohol consumption and risk of dementia in older adults. JAMA. 2003;289:1405-1413.

360 Guiraud A, de Lorgeril M, Zeghichi S, et al. Interactions of ethanol drinking with n-3 fatty acids in rats: potential consequences for the cardiovascular system. Br J Nutr. 2008 Apr 29:1-8.

361 de Lorgeril M, Salen P, Martin JL, et al. Interactions of wine drinking with omega-3 fatty acids in patients with coronary heart disease: a fish-like effect of moderate wine drinking. Am Heart J. 2008 Jan;155(1):175-81.

362 Ibid.

363 García AM, Sisternas Hoyos SP. Occupational exposure to extremely low frequency electric and magnetic fields and Alzheimer disease: a meta-analysis. Int J Epidemiol. 2008 Apr;37(2):329-40.

364 Davanipour A, Sobel E. Magnetic field Exposure: Melatonin Production; Alzheimer's Disease; Breast Cancer. Prepared for the BioInititative Working Group. July, 2007. http://www.bioinitiative.org/report/docs/section_12.pdf Accessed June 1, 2008.

365 García AM, Sisternas A, Hoyos SP. Occupational exposure to extremely low frequency electric and magnetic fields and Alzheimer disease: a meta-analysis. Int J Epidemiol. 2008 Apr;37(2):329-40.

366 Davanipour A, Sobel E. Magnetic field Exposure: Melatonin Production; Alzheimer's Disease; Breast Cancer. Prepared for the BioInititative Working Group. July, 2007. http://www.bioinitiative.org/report/docs/section_12.pdf

367 Ibid.

368 Wu Y, Feenstra M, Zhou J, et al. Molecular changes underlying reduced pineal melatonin levels in disease: alterations in preclinical and clinical stages. J Clin Endocrinol Metab. 2003;88:5898–5906.

369 Liu Zhou J, van Heerikhuize J, et al. Decreased melatonin levels in postmortem cerebrospinal fluid in relation to aging, Alzheimer's disease, and apolipoprotein E-epsilon4/4 genotype. J Clin Metab. 1999;84:323–327.

370 Brusco L, Marquez M, Cardinali D. Melatonin treatment stabilizes chronobiologic and cognitive symptoms in disease. Neuro Lett. 2000;21:39–42

371 Riemersma-van der Lek R, Swaab D, Twisk J, et al. Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. J Amer Med Assoc. 2008;299(22):2642-2655.

372 Davanipour A, Sobel E. Magnetic field Exposure: Melatonin Production; Alzheimer's Disease; Breast Cancer. Prepared for the BioInititative Working Group. July, 2007. http://www.bioinitiative.org/report/docs/section_12.pdf

373 García AM, Sisternas A, Hoyos SP. Occupational exposure to extremely low frequency electric and magnetic fields and disease: a meta-analysis. Int J Epidemiol. 2008 37(2):329-40.

Stories of Life Weave the Fabric of The Intergenerational School

Neuroscientist Peter J. Whitehouse MD PhD helps people weave the stories of their lives through memories, aspirations, and active participation in healthy living.

Whitehouse—a professor at Case Western Reserve University, medical doctor, expert in Alzheimer's disease, bioethicist, educator, author, and innovator—thinks beyond the brain as an isolated organ and into the ecology of the world and the systems that enhance prosperity and wellbeing. He is dedicating his life to ensuring that everyone, including those facing cognitive challenges, has a chance to tell personal tales of triumph and tribulation and live fully through the end of life.

Whitehouse and his wife Cathy, a psychologist, founded The Intergenerational School in 2000. The Cleveland public charter school is an award-winning institution for about 145 students in grades K-8 as well as a nurturing environment for over 30 volunteer adults and seniors.

Intergenerational School student and volunteer elder share life stories. *Photo: Peter J. Whitehouse.*

The goal of the school, located at the Fairhill Center for Aging, is to promote life-long learning keyed to developmental learning stages and "a sense of community, a sense of purpose, a sense of legacy."

A glowing profile in a U.S. Department of Education newsletter noted that in 2006 The Intergenerational School was one of just 21 high-poverty schools statewide in which 75 percent of students passed Ohio's standardized reading test. In 2007, 100 percent of third and fourth grade students passed this test.

Everyone benefits as intergenerational relationships are fostered. Young students at the school support elders by visiting, telling and listening to stories, and developing friendships at local long-term care facilities. Although many adult volunteers have memory or cognitive challenges, they mentor children in reading, arts, and hobbies and serve in such roles as library aides or technology troubleshooters. "The most important thing for the elders is that they have a sense that they are keeping their minds active," said Dr. Whitehouse.

FOOD *for* THOUGHT

The stories of the volunteers are encouraging. Mrs. Atwood, an African-American woman in her late 50s who is beginning to have memory problems (and has two sisters with Alzheimer's in nursing homes), volunteers every two weeks. She begins on Wednesday to "joyfully" plan her Thursdays at The Intergenerational School. The responsibility gives her focus and purpose. Another volunteer, Dr. Miller, holds a PhD in the history of medicine and is a relative of Moses Cleaveland who founded the Ohio city. Her participation with the children at the school helps keeps her disorientation and agitation at bay.

Danny George is Whitehouse's co-author of a recently published book, The Myth of Alzheimer's, which challenges conventional ideas about the diagnosis and treatment of Alzheimer's. George has undertaken a systematic observation of the seniors who donate their time at The Intergenerational School to evaluate how their participation benefits their health.

The success of The Intergenerational School supports the hope that we can foster the sharing of intergenerational wisdom in an increasingly complex world, and thus sustain healthy cognition throughout life. It suggests that it is possible to weave a fabric of common stories of diverse life stages that become the shared narrative of a diverse world.

LifeBook

LifeBook is an innovative program developed by Dr. Whitehouse and described in The Myth of Alzheimer's as a "practice in embracing mortality." By embracing mortality, we also embrace living fully. LifeBook helps people consider issues important at the end of life, and can provide a rich portrait of a person's life. The process suggests that people:

- Tell the story of their life – through pictures, letters and other written materials
- Envision what they want for end of life care
- Reflect on their legacy

This can be a powerful and rewarding experience and enormously helpful to the individual as well as family, friends and caregivers.

For more information, go to the www.tisonline.org and www.themythofalzheimers.com