

**ALZHEIMERS CONSENSUS CONFERENCE**

Using a literature review that resulted in a 727-page report prepared under contract by the Duke Evidence-based Practice Center, in Durham, North Carolina, a panel of medical scientists were convened at a public meeting at the National Institutes of Health on April 26-28, 2010 to study the problems of Alzheimer's and cognitive decline and make recommendations.

Two days of presentations interspersed with executive sessions of the consensus panel resulted in the preparation of a proposed statement, a structured abstract, and a post-conference news release, all of which will be mentioned in this summary.

The data for the review comes from MEDLINE® and the Cochrane Database of Systematic Reviews. Additional studies were identified from reference lists and technical experts according to the structured abstract.

In the post-conference news release, this statement appears. "Although many non-modifiable risk factors have been examined, age is the strongest known risk factor for Alzheimer's disease. Additionally, a genetic variant of a cholesterol-ferrying protein (apolipoprotein E), has strong evidence of association with the risk for developing Alzheimer's disease. Although it is hoped that improved understanding of genetic risk factors may ultimately lead to effective therapies, currently these associations are primarily useful in the clinical research setting."

The proposed statement is 25-pages long and it was developed both prior to the conference by NIH staff and during the conference by the consensus panel. At the end the statement was the subject of a news conference with questions from news organizations and the general public attending the conference.

"To date, numerous studies have attempted to describe the etiology and factors associated with the risk of development and progression of mild cognitive impairment and Alzheimer's disease; these studies have generated an abundance of theories on potential risk factors and therapies. Age is the strongest known risk factor for Alzheimer's disease, with most people diagnosed with the late-onset form of the disease after age 60. An early-onset familial form also occurs, but is rare. Genetic, cardiovascular, and lifestyle factors also have been implicated," according to the statement. Stmt, 3.

Currently, the factors causing the diseases are not supported by evidence. "There is currently no evidence considered to be of even moderate scientific quality supporting the association of any modifiable factor (nutritional supplements, herbal preparations, dietary factors, prescription or nonprescription drugs, social or economic factor, medical condition, toxins, environmental exposures) with reduced risk of Alzheimer's disease." Stmt, 5.

One serious challenge is that Alzheimer's is not uniformly defined. Vascular disease caused dementia is difficult to distinguish from Alzheimer's disease. Depression may reflect early Alzheimer's disease. Stmt., 7. A limitation of studies is causality versus association with factors. It is difficult to determine if factors of association are also a cause of the disease.

Another challenge in finding risk reduction factors is not easy, since "Cognitive decline is multicausal, and mild cognitive impairment does not inevitably lead to dementias such as Alzheimer's disease. For example, age-associated memory impairment is referenced to normal young adults and does not lead to dementia." Stmt. p.8. "For most factors, the available studies show either no association with cognitive decline or the evidence is inconclusive." Stmt. p.9. "Limitations in the evaluation of outcome include the lack of clear definition, criteria, and standardization for cognitive decline (cognitive decline is not a single entity and may have different etiologies)." *Id.*

The Statement discusses what is known about specific factors:

*"Nutritional and Dietary Factors.* The available evidence does not support a clear role for most of the nutritional and dietary factors that have been examined. The most consistent evidence is available for the longer chain omega-3 fatty acids (often measured as fish consumption) that have been shown to be associated with a reduced risk of cognitive decline in several longitudinal studies. For the other factors, the evidence varies from those studies with no association (i.e., vitamin B, vitamin E, vitamin C, folate, beta-carotene) to those with very limited evidence suggesting a possible protective effect (i.e., a Mediterranean diet)."

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*“Medical Factors.* Among the medical factors considered, a number of cardiovascular risk factors have been consistently associated with an increased risk of cognitive decline. Among these, high blood pressure has been more consistently associated, especially when relatively severe cognitive decline was examined. Diabetes also has been associated with an increased risk of cognitive decline, but this association is less consistent and appears to be more modest. Metabolic syndrome, a cluster of metabolic abnormalities associated with the incidence of cardiovascular disease, has been consistently associated with a modest risk of cognitive decline. For other medical factors, there is a lack of good quality studies (e.g., sleep apnea, traumatic brain injury) or the findings are inconclusive (e.g., obesity).”

*“Psychological and Emotional Health.* Depression and depressive symptoms have been consistently found to be associated with mild cognitive impairment.”

*“Medications.* No consistent epidemiological evidence exists for an association with either statins, antihypertensive medications, or antiinflammatories. There are insufficient data to comment on cholinesterase inhibitors or memantine. The study results are made more difficult to interpret because of variation in formulations, dosage, duration, route of administration (i.e., postmenopausal estrogens) and the drug treatment effect (i.e., antihypertensive medications).

*“Socioeconomic Factors.* Childhood socioeconomic status or cognitive milieu does not appear to be a strong influence on cognitive decline later in life. The evidence is inconsistent regarding the putative association between years of education and cognitive decline.”

*“Social and Cognitive Engagement.* The findings are inconsistent regarding living alone or being without a partner for any reason. However, there appears to be a more robust association between the loss of a spouse and cognitive decline. There is limited but inconsistent evidence suggesting that increased involvement in cognitive activities in later life is associated with slower cognitive decline and lower risk of mild cognitive impairment.”

*“Physical Activity and Other Leisure Activities.* Preliminary evidence suggests a beneficial association of physical activity and a range of leisure activities (e.g., club membership, religious services, painting, gardening) with

the preservation of cognitive function. The effect of the adoption of new activities has not been investigated.”

*“Tobacco and Alcohol Use.* There is evidence for an association between current smoking and increased risk of cognitive decline. The evidence for past smoking is less consistent. Results are inconsistent regarding the association between cognitive decline and alcohol use.”

*“Genetic Factors.* The majority of studies suggest that the presence of the ApoE e4 allele is associated with an increased rate of cognitive decline in elderly individuals, especially on some memory tasks and tasks of perceptual speed. The ApoE DNA variation does not appear to affect all cognitive domains, and there is variability between studies.” Stmt., 10-13

Treatment is really not possible with currently available products is the conclusion of the statement. Random controlled trials have failed to establish that anything works. Each of the potential areas of treatment were discussed with their associated limitations.

In terms of studies suggested for the future, there are gaps in epidemiology with an abundance of theories on modifiable risk factors and therapies. The studies that have been done do not provide strong evidence of the strength of associations and therefore cannot be used to define specific interventions. The following are the first sentences of each recommendation for future work:

- Rigorous consensus-based diagnostic criteria for Alzheimer’s disease should be developed and uniformly used across research studies.
- An objective and consensus-based definition of mild cognitive impairment needs to be developed, including identification of the cognitive areas of impairment, the recommended cognitive measures for assessment, and the degree of deviation from normal to meet diagnostic criteria.
- A standardized, well-validated, and culturally sensitive battery of outcome measures needs to be developed and used across research studies to assess relevant domains of cognitive

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functioning in a manner that is appropriate for the functional level of the population sample being studied (e.g., cognitively normal, mild cognitive impairment); and age-gender specific norms need to be established for comparison and objective assessment of disease severity.

- The caregiver is a valuable source of information about the daily function of the elderly person with mild cognitive impairment or early Alzheimer's disease, and observational studies and RCTs should collect data from caregivers in a systematic manner.
- Following the model of other chronic disease epidemiology, large-scale, long-term population-based studies using precise, well-validated exposure and outcome measures are required to generate strong evidence on biological, behavioral/lifestyle, dietary, socioeconomic, and clinical factors that may have protective or adverse effects on risk of cognitive decline or Alzheimer's disease.
- Existing cohorts from ongoing, large-scale, population-based studies—including longitudinal cohort studies of cardiovascular and noncardiovascular risk factors and outcomes, with rigorous, standardized measures of a wide range of exposures and longitudinal socioeconomic surveys that contain detailed health measures—should be explored for opportunities for timely, cost-effective identification of individuals at high risk of cognitive decline or Alzheimer's disease, provided that these outcomes are validly measured.
- Studies should include women and men from socioeconomically and ethnically diverse populations to examine the incidence and prevalence of Alzheimer's disease and cognitive decline in these groups.
- Research is necessary to identify specific population subgroups that may be at higher risk of developing cognitive impairment or Alzheimer's disease, based on nonmodifiable

factors such as age, ethnicity, or DNA variation (e.g., ApoE). Longterm studies on high-risk populations (particularly treatment-seeking individuals with symptoms of mild cognitive impairment) should be conducted to delineate risk factors for and natural progression to Alzheimer's disease and to identify the long term outcomes and factors associated with improvement, decline, and stabilization of cognitive function.

- Alternative research resources and platforms that facilitate longitudinal long-term assessments of the risk of cognitive decline and the risk of progression from cognitive decline to Alzheimer's disease need to be leveraged.
- A simple, inexpensive, quantitative instrument to assess mild cognitive impairment, which can be administered in a repeated manner by trained (nonexpert) staff in both the primary care office and the research/specialty clinic, needs to be established.
- A Web site should be established to inform the American public in an ongoing way about which preventive interventions for Alzheimer's disease and cognitive decline have proven efficacy.

The Statement ended on page 25, then listed the members of the panel members and affiliations, planning committee members and affiliations, and conference sponsors, co-sponsors and partners in another 8 pages. These sponsors (8) and partners (2) were NIH Institutes or Offices.

*NML* readers can access all of the documents mentioned here at the website:

<http://consensus.nih.gov/2010/alzmedia.htm>.

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#### EUROPEAN COURT OF JUSTICE RULES ON VITAMIN LIMITS

**R**egulation of the upper safe limits (USLs) of nutrients (vitamins and minerals) is required under Directive 2002/46. Solgar in France and others filed an action concerning the inter-ministerial decree of 9 May 2006 relating to

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nutrients which may be used in the manufacture of food supplements. On April 20, 2010 the European Court of Justice (Third Chamber) issued its judgment.

The state counsel stayed its proceedings and referred five questions to the ECJ for a preliminary ruling. The first question was: “Must Directive [2002/46], and in particular Articles 5(4) and 11(2) thereof, be interpreted as meaning that, although in principle it is for the Commission to determine the maximum amounts of vitamins and minerals present in food supplements, the Member States remain competent to adopt legislation in this field so long as the Commission has not adopted the necessary Community measure?”

The second round of four questions depended on an affirmative answer to the first question. These questions were: **(a)** If the Member States are required, in order to set those maximum amount, to comply with the provisions of Articles 28 EC and 30 EC, must they also be guided by the criteria laid down in Article 5 of Directive [2002/46], including the requirement for a risk assessment based on generally accepted scientific data, in an area in which there is still relative uncertainty? **(b)** May a Member State set maximum levels when it is impossible, as in the case of fluoride, to calculate precisely the amount of vitamins and minerals from other sources, mains water in particular, for each consumer group and on a territory-by-territory basis? May it in that case set a zero level where risks are known to exist, without resorting to the safety procedure for in Article 12 of Directive [2002/46]? **(c)** When setting maximum levels, if it is possible to take into account differences in the degrees of sensitivity of different consumer groups, as provided for in Article 5(1)(a) of Directive [2002/46], can a Member State also take into account the fact that a measure addressed solely to sections of the population who are particularly exposed to risk, appropriate labeling for example, might dissuade that group from using a nutrient that would be beneficial to it in small amounts? Might taking into account that difference in sensitivity result in the application to the entire population of the maximum level appropriate for sensitive sections of the population, in particular children? **(d)** To what extent may maximum levels be set in the case where no safe limits have been laid down because there is no established danger to health? More generally, to what extent and in what circumstances might the weighting of criteria to be taken into account lead to the setting of

maximum levels that are significantly lower than the safe limits accepted for those nutrients?

In brief, the Court answered the first question saying that Directive [2002/46] must be interpreted that, without prejudice to the Treaty, the Member States remain competent to adopt legislation on the maximum and minimum amounts of vitamins and minerals which may be used in the manufacturer of food supplements so long as the Commission has not laid down those amounts in accordance with Article 5(4) of that directive.

Each of the other questions were answered with numerous predicates and conditions, so that one should read these details carefully to determine how they may apply to situations.

The Court ruled the criteria laid down in Article 5(1) and (2) of Directive [2002/46], including a risk assessment based on generally accepted scientific data in setting the maximum amounts, must be followed while waiting on the Commission to lay down the amounts pursuant to Article 5(4).

The Court ruled a Member state may set the upper limit of a mineral by resorting to the procedure laid down in Article 12, in those cases where the amount of mineral from other sources is incalculable.

Other considerations were specified for setting levels for children and specific groups of consumers utilizing the principle of proportionality.

The Court ruled that setting limits lower than the upper safe limits cannot be excluded if the criteria of Article 5(1) and (2) are taken into account and the principle of proportionality is applied. In these later situations, the national court may be consulted on a case-by-case basis.

The judgment can be downloaded at: <http://curia.europa.eu/juris/cgi-bin/form.pl?lang=EN&Submit=Submit&numaff=C-446/08>.

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