

NIH Calls for More (and Different) Research on Preventive Measures

7 May 2010. A much greater investment in Alzheimer disease research will be needed before scientists can draw reliable conclusions about what factors increase or decrease a person's risk of developing AD, and what interventions protect against the disease. This is the sobering conclusion an expert panel convened by the National Institutes of Health (NIH) made in an April 28 [report](#) and [press release](#). The 15-member panel seated independent leaders drawn largely from outside the field of AD research itself. They examined the current evidence for a wide range of putative AD risk factors and interventions. Their verdict was not what the field, which of late has been abuzz with talk of prevention, hoped to hear. Although the panel found some consistent associations between certain risk and protective factors and AD, they judged that none of the data reached a level of scientific rigor and repeatability that would allow them to confidently make public health recommendations. This conclusion poured cold water on some much-touted associations, for example, for most dietary supplements. It also generated some controversy. To rectify the limitations of existing studies, the panel outlined an ambitious, multifaceted research agenda that includes calls for more large-scale longitudinal studies and for standardized measurements of cognitive function and risk factor exposure.

As [previous reports](#) have mentioned, the panel, drawn from the fields of gerontology, neurology, genetics, and nutrition, evaluated 25 reviews and 250 primary research studies, including both observational studies and randomized clinical trials (RCTs). To be considered, studies had to meet criteria that included a duration of one year or greater, 300 or more participants for observational studies, and 50 or more participants for RCTs. The reviewers evaluated nutritional factors, medical conditions, medications, social/economic/behavioral factors, environmental factors, and genetics. They used a grading system that rated the level of evidence for each finding as high, moderate, or low, with "low level of evidence" indicating that further research might change the estimate of a factor's effect.

The reviewers found only a few factors that showed a consistent association with AD or cognitive decline. The strongest associations, for which the panel graded the level of evidence as moderate, showed an increased risk of AD associated with carrying the ApoE4 gene, and from taking conjugated equine estrogen combined with progesterone (not estrogen alone). Diabetes, depression, and current tobacco use were consistently associated with an increased risk of AD, while physical activity, a Mediterranean diet (low in saturated fat, high in grains, fruits, vegetables, nuts, fish, and olive oil), and high levels of cognitive engagement were consistently associated with a decreased risk of AD (e.g., [Féart et al., 2009](#); [Willis et al., 2006](#)). For all of these factors, the panel graded the level of evidence as low. The panel found a high level of evidence that taking ginkgo biloba does not alter AD

risk, and moderate evidence that vitamin E has no effect on AD risk.

A low level of evidence does not mean the studies are of poor quality, said Neil Buckholtz, who heads the Dementias of Aging Branch at the National Institute on Aging (NIA), but rather indicates that “we don’t yet have enough information to make specific recommendations.” These studies point to the most fertile areas to investigate, Buckholtz said. “We have to now firm up those data and those kinds of associations in further research.”

The panel identified several problems with the existing data. There are too few RCTs, considered the gold standard of research trials; many studies are too short, often lasting less than one year; and a lack of standardization makes comparison of outcomes across studies impossible. The panel urged the field to develop standardized, validated measures for risk factors and interventions that take into account the intensity, duration, and timing of exposure, as well as standardized methods for cognitive assessment. Because of the long prodromal phase of AD, during which no symptoms are seen, the panel recommended that exposure to risk factors be studied much earlier in life, years prior to the expected onset of symptoms, and that interventions should also be begun as early as possible.

It is too early to tell whether the panel’s report will prompt specific changes in NIA funding, but Buckholtz suggested that funding for epidemiological studies might become more of a priority. Some of the proposed changes are already in progress, Buckholtz said. The [NIH Toolbox Project](#) seeks to develop standardized measurements of cognitive function that could be used in future studies. The 29 NIA-funded Alzheimer’s Disease Centers collect uniform data, available from the [National Alzheimer’s Coordinating Center](#), so that investigators can compare measures across centers. More reliable measurements of disease such as imaging and fluid biomarkers are being incorporated into more studies, thanks to projects such as the [Alzheimer’s Disease Neuroimaging Initiative \(ADNI\)](#). Looking to the future, long-term, large-scale epidemiological studies similar to the [Framingham Heart Study](#) will be particularly important for collecting better data on AD risk and protective factors, Buckholtz said, but “these are big studies, they cost a lot of money, they go on for a long time. We try to fund as many of them as we can, but it’s difficult.”

Lack of funding is the main issue holding back progress, says the Alzheimer’s Association, which issued a [statement](#) supporting the NIH panel’s call for more research. “The research dollars allocated today don’t even come close to reflecting the actual public health need,” said the Association’s representative, Maria Carrillo. She pointed to the progress a sizable investment in research has made in other health areas, such as stroke and some cancers. “It’s time to really pay attention to Alzheimer disease research.” The Association is sponsoring the [Alzheimer’s Breakthrough Act](#), which calls for \$2 billion in AD funding, roughly a quadrupling of current research dollars. The bill was referred to the House Energy and Commerce Committee by its sponsor, Ed Markey, where it has languished since July 2009.

But the Alzheimer’s Association took issue with the NIH panel’s conclusion that current research is inadequate to make health recommendations. “The Association continues to

stand by our [brain health recommendations](#),” Carrillo said, which include staying physically, socially, and mentally active, and adopting a brain-healthy diet. “We do feel that some of the retrospective and epidemiological studies that have been done give us some good indications that brain health can make a difference in our future in terms of Alzheimer’s risk.”

For people concerned about AD risk, Buckholtz said, the panel’s report “is suggestive that there are some things you can do, in terms of a healthy diet, a healthy lifestyle.” He recommended physical exercise, social interactions, reducing high blood pressure and high cholesterol, and making lifestyle choices that reduce the risk of diabetes and cardiovascular disease. These lifestyle choices, Buckholtz said, “can certainly help maintain a healthy brain.”—Madolyn Bowman Rogers.

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Comments on News and Primary Papers

Comment by: [Kenneth Kosik, ARF Advisor](#) Submitted 20 May 2010 Posted 20 May 2010

The NIH State-of-the-Science Conference has set a threshold of evidence required to make recommendations that goes beyond what would best serve the interests of public health. This may seem paradoxical, because as scientists we demand the highest standards of rigor, and critiquing the panel for setting the bar too high may appear to undermine our strong commitment to the scientific method. However, AD prevention simply is not at the point yet of delivering formal proof as per the dictums of evidence-based medicine. Even so, this panel is likely to influence the thinking of policymakers, who routinely operate in a situation of having to make far-reaching decisions in the absence of definitive proof. Hence, policymakers require guidance that has the public health interest at heart.

The expectation that interventions such as treating hypertension, adopting good nutrition, and exercise require the same standard of proof as demonstrating efficacy and safety of a novel drug represents a further setback for the already arduous task of gaining widespread adherence to healthy behaviors. How would we obtain that standard of proof? The NIH panel does not seriously believe that we will conduct trials in which subjects will be randomized to a control group who do not treat their hypertension, follow a poor diet, or refrain from exercise. And even if we found a clever study design, how would the panel stratify for the multiple variables we encounter in all lifestyle studies? Stratification for a myriad of diets, many levels and types of exercise, a large number of anti-hypertensive treatment regimens, and, most challenging, genotype, would require statistical power that exceeds Earth’s population.

Furthermore, the goals of our communities are to prevent dementia rather than to focus on efficacy in a single cause of dementia, Alzheimer disease. The very large contribution of small vessel disease to the dementia phenotype is completely overlooked when the only outcome measure upon which we base recommendations is strictly Alzheimer’s. Ironically, the panel did note health disparities in the occurrence of dementia, but failed to draw the conclusion that the

very groups who suffer most also have a higher incidence of hypertension, poor nutrition, and lack opportunities to exercise.

The panel would have served the nation better had it acknowledged that we have achieved a reasonable level of certainty to recommend risk reduction through safe interventions such as eating well, exercise, and the treatment of hypertension. This is sound both scientifically and from a public health standpoint. Risk reduction does not make the same claim as prevention and allows us to pursue more actively the vital public health efforts directed toward nutrition and obesity in our schools, toward health disparities due to the absence of fresh foods in poor inner city communities, and toward the incontrovertible value of exercise for general well-being. As a scientist, I readily concur that the repertoire of laboratory techniques, which ranges from genetically identical mouse strains to precise quantitative assessments of plaques and tangles and their correlations with advanced imaging procedures, is extraordinarily insightful. But as a physician and member of the community, I think it remains crucial that we not conflate these rigorous approaches, essential as they are to scientific progress, with the best interests of the community now. We have to work for the public good even while we have a less-than-complete dataset.