

Why so negative about preventing cognitive decline and dementia? - The jury has already come to the verdict for physical activity and smoking cessation

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The world is ageing rapidly and accompanying this demographic transition will be a significant increase in the number of people with dementia, a condition that will more greatly affect the developing world, rather than the developed world, in both absolute numbers and proportionate increase.[1] The human and financial costs of this condition have, not surprisingly, been of concern to older people, their families and policy makers around the world as they grapple with what will eventually be a major cause of life years lost to disability. The search is on for safe, effective and hopefully, affordable ways to prevent this common and devastating condition of older people.

Against this background, it was timely for the U.S. Department of Health and Human Services National Institutes of Health to host a consensus conference on “Preventing Alzheimer’s Disease and Cognitive Decline”, [2] supported by an Evidence Based Review. [3] Many of the other scourges of old age have already demonstrated a reduction in age specific incidence and thus there is hope that similar outcomes may be achieved for dementia. For example, there has been a 25% reduction in age-adjusted stroke death rates in the United States, [4] an observation confirmed in Australia where further data indicate that this is more likely to be due to a decreased incidence of stroke rather than an improvement in survival following a stroke. [5] Similarly, after an earlier increase, age adjusted female hip

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fracture incidence decreased between 1995 and 2005 by about 25%.[6] Therefore, prevention of these common problems of older people may be achievable and a goal for which it is worth striving. The degree of difficulty in ascertaining the population prevalence and incidence of dementia, and also that many of the higher quality studies were completed over two decades ago, makes it unlikely that any secular trend in incidence of dementia would have been detected. The fact that we are uncertain as to exactly why the incidence of stroke and hip fractures has decreased has not deterred the ongoing search for modifiable risk factors and interventions in these conditions, and nor should it in the commonest cause of severe disability in older people - dementia.

So what were the conclusions of this consensus conference? Not a lot. Firstly, the title of the conference was a little disappointing in itself as all that is dementia is not Alzheimer's Disease (AD), particularly in the very old.[7] As growing numbers of people of advanced age underly the large increase in the number of people with dementia, it is likely that the proportion of people with dementia due to AD will decrease in the future, and many of these people with dementia will have mixed pathology. One of the criticisms the consensus panel leveled at the vascular risk factor hypothesis was "it can be quite difficult to disentangle the factors associated with Alzheimer's disease because of their contribution to vascular disease and related dementias and those that are truly associated with Alzheimer's disease". Surely with our increased understanding of the role of vascular factors in the progression of AD this is putting too fine a point on this issue. The more important question is whether the treatment of vascular factors results in decreased rates of dementia, including AD and the amount of cognitive decline. The best evidence for treatment of vascular risk factors lies in the use of anti-hypertensives where there is considerable uncertainty as to what the RCT evidence already has demonstrated but the comment from the Evidence Based Review[3] appeared far too negative. A recent systematic review[8] which included one additional randomized trial to the Cochrane meta-analysis[9] demonstrated a 13% reduction in the rate of incident dementia with the use of antihypertensives. This may be the best evidence that we will ever obtain on this subject due to the bias to the null hypothesis because of the large number of control subjects who require treatment with antihypertensives, and the experience from the HYVET study[10] that these trials are no longer able to be performed in the developed world because of the understandable reluctance of clinicians to randomize hypertensive older people to placebo, when effective antihypertensives are readily available.

Perhaps the most worrying part of the consensus statement concerned the very negative view of the effect of modifiable lifestyle factors, for two of which there is already good evidence for individuals to make judgments. The first of these is smoking. Initially smoking, based on case control studies, was considered a protective factor for the development of AD but a review of the cohort studies found an elevated risk.[11] This finding is supported by a recent systematic review [12] of cohort studies which demonstrated an increased risk of 1.79 (95% CI 1.43–2.23) for incident AD. In addition brain imaging has provided confirmatory evidence. In a study examining older smokers without discernible cognitive changes, smokers were found to have decreased grey matter density in the posterior cingulate and precuneus, right thalamus and frontal cortex compared with non-smokers, similar abnormalities to those found in people with early AD.[13] Because of ethical concerns, there will be no randomized trials evaluating this risk factor, but AD, and a multitude of other

diseases, can have their incidence decreased by quitting smoking. It is difficult to dismiss this evidence, as the NIH statement does, as being “of low quality”.

The evidence for physical activity seemed also to be discounted too cursorily for what is now a large and relatively consistent pool of animal and human data. Animal studies support the concept of plasticity of the human brain and that many molecular and cellular pathways may be involved in neurogenesis and other exercise induced structural and functional brain changes. [14,15] Observational data across the life course support the benefits of physical activity, particularly aerobic activity in improving cognition.[16] There are even more data than the Evidence Based Review mentioned. The Duke Team[3] who reviewed 12 cohort studies and found that physical activity lowered the risk by 30% of incident AD. A recent review summarized observational data of 14 studies, contained data on 27,255 participants of which 2731 had a diagnosis of dementia or AD.[17] The pooled relative risk for overall dementia in the highest physical activity category compared with the lowest was 0.72 (95% CI 0.60–0.86), and for AD 0.55 (95% CI 0.36–0.84). These observational data are very consistent with a lowering of risk with increased physical activity, but because reverse causality may be an issue, i.e. those people who are in better cognitive health may choose greater levels of physical activity, confirmation by randomized trials is essential.

Ideally trials of increased physical activity should be examined against the outcome of incident AD but no such studies exist, and they would by necessity require large numbers, for a prolonged period of follow-up, and therefore be very expensive. However, there are now many trials of physical activity in humans with a diverse range of cognitive outcomes and a more modest set of brain changes. Besides the Cochrane review[18] referred to in the Evidence Based Review there have been other reviews which have included other studies which also find cognitive benefits. [16] The Cochrane review found improvements in motor function and auditory attention in the groups randomized to aerobic physical activity whereas other reviews have found benefits in executive functions.[19] There have been several other recent RCTs only one of which[20] was identified by the Evidence Based Review. That study examined 170 participants with memory complaints who were randomized to a 24-week home-based program of physical activity. Participants in the intervention group improved 1.3 points (95% confidence interval, (CI) –2.38 to –0.22) on the main outcome measure of the Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) and this improvement was maintained for 12 months after the completion of the intervention with some other benefits demonstrated in memory. Another study of aerobic exercise in subjects with mild cognitive impairment aged 70 to 80 years found trends for effects in improving memory and attention over a 12 months period.[21] Another moderately large study of progressive resistance training has added further complexity to these issues.[22] This study found benefits in women aged 65 to 75 years of age with training designed to increase strength as opposed to aerobic ability. These cognitive benefits were mainly found in executive functioning. Other randomized controlled trials have found benefits in brain structure and function as well as improvements in cognition as a function of 6 and 12 month aerobic training programs.[23–25]

Thus there is now good evidence that the use of antihypertensive medication, cessation of smoking and increasing physical activity produce cognitive benefits in older people. Because

of ethical concerns randomization to control groups are already difficult to perform for trials of antihypertensive medications and quitting smoking. The evidence for increased physical activity spans animal studies, observational and randomized trials in humans and the evidence is quite consistent. In a country which has deemed boldness to be a virtue, it is difficult to understand why the NIH consensus statement has taken such a cautious approach.

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