Nutrigenetics and Cognitive Health

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Life expectancy (LE) continues to rise dramatically, as reinforced by the latest Global Burden of Disease Study statistics published in December 2012 in *The Lancet* (Table 1).[1] Between 1970 and 2010, LE increased in 179 of the 187 countries included, with LE at birth increasing 3 to 4 years per decade since 1970.

Table 1: Worldwide Life Expectancy Data for Males and Females 1970-2010[1]

	Male Life Expectancy					Female Life Expectancy				
	1970	1980	1990	2000	2010	1970	1980	1990	2000	2010
World	56.4 (55.5-57.2)	59.8 (59.2-60.2)	62.8 (62.3-63.3)	64.2 (63.6-64.6)	67.5 (66.9-68.1)	61.2 (60.2-62.0)	64.9 (64.3-65.4)	68.1 (67.6-68.6)	69.8 (69.3-70.2)	73.3 (72.8-73.8)

Source: Wang H et al. Age-specific and sex-specific mortality in 187 countries, 1970-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2071-2094. Reprinted by permission of Elsevier.

However, this apparent public health success story in increased LE is not matched by an increase in healthy life expectancy (HLE), with an estimated 0.8-year increase in HLE for every 1-year increase in LE. Therefore, although individuals are living longer, they are sicker for longer. This is very apparent when looking at US statistics, with increases of 4.2 years and 2.7 years in LE and HLE, respectively, in males between 1990 and 2010.[2]

Given the almost exponential association between age and cognitive decline, these aging population demographics are having dramatic impacts on dementia incidence worldwide, with the prevalence approximately doubling every 20 years and estimated to increase to 115 million by 2050.[3]

Existing drugs for Alzheimer's disease (AD), the most common form of dementia, do provide medium-term symptomatic benefits, but currently no approved disease-modifying therapies are available.[4] Given the "explosion" in dementia incidence and the recent high-profile failures of various novel disease-modifying drugs in clinical trials, the development of effective lifestyle strategies to preserve cognition would prove extremely timely, providing enormous health, social, and economic benefits.

Data that allow an estimation of the public health impact of delayed disease onset in the area of dementia and AD are notably absent. However, available data suggest that at a population level, a modest 2-year delay in onset would reduce population incidence by 22% by 2050, resulting in 25 million fewer cases worldwide.[5] The

public health benefits are possibly even greater if effective lifestyle strategies are targeted at high-risk individuals, such as those with mild cognitive impairment (MCI) or an apolipoprotein E4 (*APOE*-ε4) genotype.

Omega-3 Fatty Acids and Cognitive Health

The cardiovascular benefits of the omega-3 fatty acids found in fish, namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are well established. Typical current population recommendations of an intake of >0.5 g/day of EPA+DHA, increasing to >1 g/day in individuals with diagnosed cardiovascular disease, are based largely on these known benefits to the heart and systemic circulation. The brain is highly enriched in DHA, constituting 15% to 25% of total fatty acids, compared to <5% in most other body tissues. DHA performs numerous structural and metabolic roles, particularly at the neuronal synaptic region.

Although data from "fit-for-purpose" human randomized controlled trials (RCTs) are currently limited in the area of cognitive health, a relatively large body of animal and human cross-sectional and prospective data demonstrates that low dietary fish intake (EPA and DHA), and resultant low omega-3 fatty acid status, are associated with neurocognitive dysfunction and a greater risk of cognitive decline and dementia.[6-8]

For example, in the Framingham Cohort, individuals in the top quartile of plasma DHA had a 47% reduced risk of developing dementia, compared to those in the bottom quartile.[7] In addition, lower plasma and red blood cell EPA and DHA levels are associated with smaller brain volumes and atrophy of regions associated with dementia, such as the medial temporal lobe.[9,10]

Findings from available RCTs are somewhat mixed, but they suggest the greatest benefit of fish oil (EPA+DHA) or DHA supplementation in individuals with MCI but without a clinical diagnosis of AD.[11] The lack of efficacy in the largest published RCT (UK-based Older People and n-3 Long-Chain Polyunsaturated Fatty Acids Study [OPAL] 2-year intervention, n=867) may be partly because of the inclusion of regular fish consumers, with 92% of participants consuming fish ≥1 serving/week.[12] This pattern of fish consumption is atypical for a UK population, resulting in the overrepresentation of regular fish consumers. For these individuals, habitual omega-3 intake is perhaps close to optimal, making it difficult to achieve further benefits because the intervention dose was modest (700 mg/day).

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Well-powered human RCTs that use sensitive state-of-the-art measures of cognitive function and brain imaging to assess efficacy are greatly needed in individuals with a low habitual EPA/DHA intake and compromised EPA/DHA status (majority of UK and US adults). These are the individuals most likely to respond and benefit.

APOE Genotype and Cognitive Health

Originally described for its role in lipid transport (it is the almost exclusive lipid transporter in the brain and central nervous system), apolipoprotein E (apoE) is pleiotropic. Its role in brain and neuronal function is summarized in the following Figure.

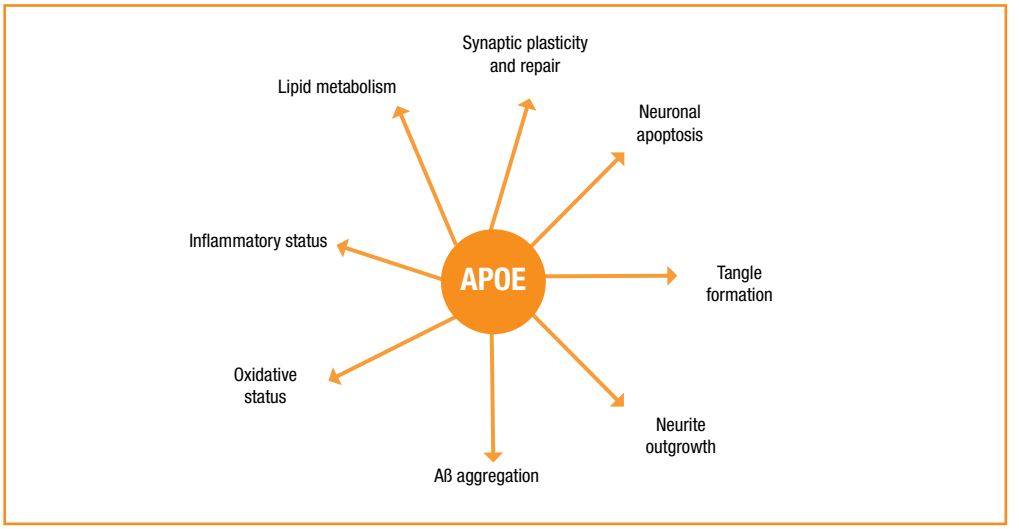

Figure. Role of apoE in neuronal function.

Aβ=amyloid beta, apoE=apolipoprotein E

APOE-ε4 genotype is a highly significant genetic risk factor for AD, increasing risk ≈4- and 15-fold in carriers of either a single (20% to 25% Caucasians) or double (1% to 2% Caucasians) copy of the risk allele, compared to *APOE*-ε3 homozygotes (Table 2).[13] Importantly, an *APOE*-ε4 genotype is associated with a 2-fold higher conversion rate from MCI to AD[14,15] and an earlier age of AD onset.[16] Therefore, in an era of a gradual move toward the provision of stratified preventative and therapeutic targets based on genetic make-up,[17] *APOE*-ε4 carriers represent a large population subgroup that would particularly benefit from targeted strategies that may prevent or delay disease onset.

Table 2. Impact of *APOE* genotype on Alzheimer's Disease Incidence[13]
(data presented as odds ratios (ORs) with 95% confidence intervals (CI) in parentheses)

Study	ε3ε4 vs ε3ε3 (95% CI)	ε4ε4 vs ε3ε3 (95% CI)	ε2ε3 vs ε3ε3 (95% CI)	ε4 vs ε3 (95% CI)	Total sample size (number of independent samples)
Farrer et al[18,a,b]					
Caucasian, clinic/autopsy	3.2 (2.8-3.8)	14.9 (10.8-20.6)	0.6 (0.5-0.8)	Not reported	6305 (31)
Caucasian, population-based	2.7 (2.2-3.2)	12.5 (8.8-17.7)	0.6 (0.5-0.9)	Not reported	4858 (10)
Asian (Japan)	5.6 (3.9-8.0)	33.1 (13.6-80.5)	0.9 (0.4-2.5)	Not reported	2313 (5)
AlzGene[c]					
Caucasian, clinic/autopsy	4.3 (3.3-5.5) $P<1 \times 10^{-16}$	15.6 (10.9-22.5) $P<1 \times 10^{-16}$	0.6 (0.3-1.2) $P=0.1$	4.1 (3.5-4.8) $P<1 \times 10^{-16}$	4946 (20)
Caucasian, population-based	2.8 (2.3-3.5) $P<1 \times 10^{-16}$	11.8 (7.0-19.8) $P<1 \times 10^{-16}$	0.3 (0.2-0.6) $P=4.6 \times 10^{-7}$	3.2 (2.7-3.8) $P<1 \times 10^{-16}$	2866 (8)
Asian (Japan)	3.9 (1.9-8.0) $P=0.0002$	21.8 (8.6-55.3) $P=1.1 \times 10^{-16}$	0.7 (0.3-1.6) $P=0.3$	4.0 (2.9-5.5) $P=1.1 \times 10^{-16}$	1541 (4)

[a]Based on pooled genotypes and adjusted for age and study. ORs and total sample sizes are taken from Table 3 of Farrer et al[18] and the number of independent samples from Table 1 of Farrer et al.[18]

[b]*P* values were not reported for the effect size estimates in Farrer et al.[18]

[c]Based on study-specific crude ORs, using random-effects models on published genotypes only. Studies, choice of ethnic group, and ascertainment scheme are based on information provided in Farrer et al.[18]

Source: Bertram L et al. Systematic meta-analysis of Alzheimer disease genetic association studies: the AlzGene database. *Nat Genet.* 2007;39(1):17-23. Reprinted by permission of Nature Publishing Group.

The Road Ahead: Nonreductionist Approach to Cognitive Health

Traditionally the reductionist approach in nutrition research has focused on establishing the impact of individual foods, food groups, or dietary components on specific health end points. Because the neural processes involved in cognitive health and decline are complex, a combination of nutritional compounds may prove most efficacious. However, few studies have adapted this approach. As recently reviewed,[19] accumulating knowledge on the physiological and molecular targets for individual dietary constituents provides strong justification for the cosupplementation of a number of components, which individually may have only modest benefits.

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