~75% of health care costs are for aged

X 80 million US aging baby boomers
US MEDICARE COST DEFICITS PROJECT TO $ 52 Trillion
Will require a 122% payroll tax increase

CONCLUDE: Prevention approaches are essential to optimize, including diet and exercise
If you’re fat, get fit

**TABLE 4. Multivariate Proportional Mortality Hazard Ratios (HRs) by Body Mass Index (BMI) and Fitness in Study Participants**

<table>
<thead>
<tr>
<th>Fitness category</th>
<th>No. of men</th>
<th>No. (%) of deaths</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI &lt;18.5 (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low fitness</td>
<td>48</td>
<td>37 (77)</td>
<td>4.48 (3.06-6.57)</td>
</tr>
<tr>
<td>Moderate fitness</td>
<td>83</td>
<td>46 (55)</td>
<td>3.09 (2.17-4.38)</td>
</tr>
<tr>
<td>High fitnessd</td>
<td>6</td>
<td>0 (0)</td>
<td>...</td>
</tr>
<tr>
<td><strong>BMI 18.5-24.9 (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low fitness</td>
<td>543</td>
<td>259 (48)</td>
<td>2.03 (1.60-2.58)</td>
</tr>
<tr>
<td>Moderate fitness</td>
<td>1779</td>
<td>526 (30)</td>
<td>1.65 (1.34-2.04)</td>
</tr>
<tr>
<td>High fitness</td>
<td>563</td>
<td>69 (12)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td><strong>BMI 25.0-29.9 (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low fitness</td>
<td>800</td>
<td>330 (41)</td>
<td>1.79 (1.43-2.25)</td>
</tr>
<tr>
<td>Moderate fitness</td>
<td>3471</td>
<td>724 (21)</td>
<td>1.15 (0.93-1.42)</td>
</tr>
<tr>
<td>High fitness</td>
<td>916</td>
<td>60 (7)</td>
<td>0.43 (0.32-0.59)</td>
</tr>
<tr>
<td><strong>BMI ≥30.0 (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low fitness</td>
<td>776</td>
<td>272 (35)</td>
<td>1.61 (1.27-2.03)</td>
</tr>
<tr>
<td>Moderate fitness</td>
<td>3042</td>
<td>454 (15)</td>
<td>0.99 (0.80-1.23)</td>
</tr>
<tr>
<td>High fitness</td>
<td>390</td>
<td>24 (6)</td>
<td>0.52 (0.34-0.82)</td>
</tr>
</tbody>
</table>

**Fig. 1** Trends in the BMI-mortality association according to age-group and gender. Twenty years cumulative mortality in different BMI-groups for men and women in three different age-strata (continuous line for women, dashed line for men).

- Increased mortality in the slim elderly: a 42 years follow-up study in a general population- Gulsvik et al 2009
Dietary n-3 fatty acids and Alzheimer Disease: Does the source matter?

FAT IN YOUR HEAD: GOOD OR BAD?

18:n-2 >> C20:4 > PGs
diet membrane COX T
NSAIDs

cPLA2

Your brain evolved to decide “What’s for lunch?”

6th International Congress on Vegetarian Nutrition
Sun Feb 24, 20013

Greg M. Cole, Ph.D. Prof Medicine and Neurology, UCLA
Assoc Director, GLA VA GRECC and UCLA Alzheimer Center

Loma Linda, Ca
Pathology causing cognitive deficits?
Taoists (tangles) vs Baptists (plaques)
or "Invisible" Aβ oligomer toxins in the middle?

Monomer → Dimer → Trimer → Oligomer/Protofibril → Amyloid fibril

Insoluble Toxic Deposit
In early AD, Mutations Implicate $\text{Ab}_42$

$70\%$ of AD cases unexplained, likely polygenic & "weak" and likely modulated by environment
DHA (C22:6, n-3) and AD

- Essential fatty acids:
  - Linoleic acid (18:2 n-6) >>> Arachidonic acid (ARA, n-6 series)
  - Linolenic acid (18:3 n-3) >>> Docosahexanoic acid (DHA, n-3)
- n-6 pro-inflammatory, n-3 are anti-inflammatory
- Ratio of n-6/n-3 or ω-6/ω-3 is optimal near 4:1.
- DHA is very high in brain (~31% of FA in PE in cortex)
- Six double bonds make it most susceptible to oxidative attack, but reduces oxidative damage in vivo.
- DHA (fish, algae) is crucial in brain/retina development and CNS maintenance in adults
- Fish/ DHA consumption reduces AD risk by about half (most recent Framingham study-)
Framingham Study~50% Risk Reduction for AD with higher plasma DHA (> 2 servings fish/ wk)

- 1. 3 - 1.8 fish servings/ wk ( ~100 mg/ d DHA) quartiles 1 and 2 vs
- 3 fish servings/wk ( ~180 mg/d DHA) in quartile 4 ( > 4.2% PC-DHA plasma)

Reduced dementia with higher plasma PC-DHA in Framingham study
Eating fish reduces risk of AD  (RSNA 2011)

Raji et al 2011 scanned 260 cognitively normal subjects at risk for AD in the Cardiovascular Health Study and compared the 163 with regular weekly fish consumption 10 yrs prior to scans

“Greater hippocampal, posterior cingulate and orbital frontal cortex volumes in relation to fish consumption reduced the risk for five-year decline to MCI or Alzheimer's by almost five-fold.”
Omega-3/ fish generally associate with reduced cognitive decline/ dementia/ AD (17/21 studies)

- Kalmijn et al 1997 Ann Neurol (Rotterdam)
- Conquer et al 2000 Lipids (Canada)
- Heude et al 2003 Br. J. Nutrition (France)
- Morris et al 2003, 2005 Arch Neurol. (Chicago)
- Kalmijn et al 2004 Neurology (Holland)
- Dullemeijer et al Am J. Clin Nutr. 2007 (Holland)
- Barberger-Gateau et al Neurology 2007 (French)
- Wang et al 2008 J Alz Dis. (Oregon)- correlate MMSE with omega-3 index in RBC
Of particular importance, properly designed randomized clinical trials that are sufficiently powered and of an adequate length (e.g. three to five years of follow-up) need to be conducted for dementia, especially Alzheimer's disease, as distinct from vascular dementia.

Given the concern described above regarding the possible difficulty of conducting valid studies on dementia, due to a lengthy presymptomatic latency period, it would be of interest to conduct intervention clinical trials of omega-3 fatty acids in middle-aged adults as well as in populations of cognitively-impaired adults prior to a dementia diagnosis, such as individuals with various sub-types of mild cognitive impairment (MCI).
USA is high n-6 & DHA Deficient

<table>
<thead>
<tr>
<th>Diet/Location</th>
<th>% DHA</th>
<th>% ARA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudan</td>
<td>0.07</td>
<td>0.50</td>
</tr>
<tr>
<td>Midwest, AZ, BC (Auestad)</td>
<td>0.12</td>
<td>0.51</td>
</tr>
<tr>
<td>Pastoral China</td>
<td>0.14</td>
<td>1.22</td>
</tr>
<tr>
<td>Netherlands</td>
<td>0.19</td>
<td>0.34</td>
</tr>
<tr>
<td>Germany</td>
<td>0.23</td>
<td>0.45</td>
</tr>
<tr>
<td>Australia</td>
<td>0.26</td>
<td>0.45</td>
</tr>
<tr>
<td>Texas (Birch)</td>
<td>0.29</td>
<td>0.56</td>
</tr>
<tr>
<td>France</td>
<td>0.32</td>
<td>0.50</td>
</tr>
<tr>
<td>Enfamil LIPIL</td>
<td>0.32</td>
<td>0.64</td>
</tr>
<tr>
<td>Spain</td>
<td>0.34</td>
<td>0.50</td>
</tr>
<tr>
<td>Nigeria</td>
<td>0.34</td>
<td>0.56</td>
</tr>
<tr>
<td>Israel</td>
<td>0.37</td>
<td>0.58</td>
</tr>
<tr>
<td>Rural China</td>
<td>0.68</td>
<td>0.80</td>
</tr>
<tr>
<td>Urban China</td>
<td>0.82</td>
<td>1.01</td>
</tr>
<tr>
<td>Japan</td>
<td>1.00</td>
<td>0.40</td>
</tr>
<tr>
<td>Marine China</td>
<td>2.78</td>
<td>1.17</td>
</tr>
</tbody>
</table>

We get ~50-100 mg/ DHA day while expert panels recommend 200-300 mg per day

DHA is added to infant formula to help retina & brain development.
Cerebral Metabolism in AD where synapses are lost resembles Infants where few synapses have formed

Normal  Early Alzheimer's  “Senile”  infant
ALA intake reduces decline?

1) a non-significant 30% lower risk of AD in top quintile of ALA intake (median: 1.46 g/d), n= 815 Chicago Healthy Aging, 4 years (Morris et al 2003)

2) lower ALA levels in demented vs non-demented InChianti Study (0.34% vs 0.39%, P < .05) (Cherubini et al 2007)

3) Lower RBC ALA levels were inversely associated with cognitive decline, n= 246, 4 years French Eva study (Heude et al. 2003).

4) Reduced decline with flaxseed oil supplements (Wash U, NAAC study 2013 unpublished).

5) 50 AD patients assigned to a mix of ALA and linoleic acid ("SR-3", 0.5 mL/d) had significant effects on short-term memory after 4 weeks compared to 50 patients on placebo Yehuda et al 1996
Plant Sources of Omega-3

Nicohols et al 2010 Nutrients 2:572

Dupont, monsanto-
Soy beans

BASF -
mustard

Land Plants

16:0 → 18:0 → 18:1 → 18:2 → α-18:3

Δ6-des

18:4 SDA

Δ6-elo

20:4

Δ5-des

20:5 EPA

Δ5-elo

22:5

Δ4-des

22:6 DHA

Marine Algae
• Low estimated daily DHA used by brain
• Rapaport et al 2011 Prostaglandins
“Souvenaid” - Fish oil + Vit BEC etc

- P. Scheltens et al 2012, JAD Efficacy of Souvenaid in Mild AD
- 2nd positive trial

Table 1
Nutritional composition of Fortasyn™ Connect, the nutrient combination in Souvenaid

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount per daily dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eicosapentaenoic acid, mg</td>
<td>300</td>
</tr>
<tr>
<td>Docosahexaenoic acid, mg</td>
<td>1200</td>
</tr>
<tr>
<td>Phospholipids, mg</td>
<td>106</td>
</tr>
<tr>
<td>Choline, mg</td>
<td>400</td>
</tr>
<tr>
<td>Uridine monophosphate, mg</td>
<td>625</td>
</tr>
<tr>
<td>Vitamin E (alpha-tocopherol equivalents), mg</td>
<td>40</td>
</tr>
<tr>
<td>Vitamin C, mg</td>
<td>80</td>
</tr>
<tr>
<td>Selenium, µg</td>
<td>60</td>
</tr>
<tr>
<td>Vitamin B12, µg</td>
<td>3</td>
</tr>
<tr>
<td>Vitamin B6, mg</td>
<td>1</td>
</tr>
<tr>
<td>Folic acid, µg</td>
<td>400</td>
</tr>
</tbody>
</table>

*Souvenaid (125 mL [125 kcal] daily dose) contains Fortasyn Connect. Souvenaid is a registered trademark of Nutricia N.V. Fortasyn is a trademark of Nutricia N.V.
ALA intake has no effect?

1) no effect, Canadian Study of Health and Aging (Kroger et al 2009)

2) lower ALA levels in demented vs non-demented InChianti Study (0.34% vs 0.39%, P < .05) (Cherubini et al 2007)

3) Lower RBC ALA levels were inversely associated with cognitive decline, n= 246, 4 years French Eva study (Heude et al. 2003).

4) Reduced decline with flaxseed oil supplements (Wash U, NAAC study 2013 unpublished).

JURY STILL OUT!
Alpha Omega Trial Fails?

- 400 mg/d EPA-DHA, 1.9 g/d ALA or placebo for 40 mos fails to prevent arrhythmias/ 2\textsuperscript{nd} M.I.
- No impact on cognitive decline for either omega 3 (Geleijnse et al 2012)
Nutrient biomarker patterns, cognitive function, and MRI measures of brain aging. Bowman et al 2012

- Higher intake of vitamins BCDE correlate with larger brain volume.
- Higher marine LC-FA (But not ALA) intake Correlates with lower WMH.
Omega-3 fatty acids improve the diagnosis-related clinical outcome. Heller et al 2006 Crit Care Med

Fish oil increased severe head injury survival by ~50%
Hypothesis: ROS will oxidize DHA which will increase ROS, a positive feedback loop. Aggravated by low dietary DHA and low dietary antioxidants in the Western diet. Calon et al, Neuron -04.
Omega-3 Fatty Acids and Lipoic Acid in Alzheimer’s Disease- Shinto et al al-08
Neurology vol 70(11) Supplement 1: A393 2008

- 3 groups, randomized, double-blind, 1 yr, placebo-control trial, >55 yrs., probable AD (MMSE 15-26):
  - 1. placebo,
  - 2. omega-3 (3 gms fish oil = 750 mg DHA, 1050 mgs EPA)
  - 3. omega-3 plus 600 mg Lipoate.
- Results MMSE stabilized with group 3 (p=0.02)
- Activities daily living improved in both omega-3 groups (p=0.005)
Mediterranean Diet and Exercise
Scarmeas et al JAMA 2009

- 1880 subject New York community study
- Med Diet reduces dementia risk
- DHA + exercise
- DHA in diet correlates with low Abeta 42 in plasma
“What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?”
DHA and Exercise Reduce Tau Pathology in Pure Tangle Model

- Untreated htau Tg mice accumulate tau/tangles (leading to synaptic marker and neuron loss) by 17 mo
- Treated from 10-12 to 16-18 mos with: Exercise wheels, α-lipoate (ALA), Exer + ALA, DHA or DHA + Exer
Clinical Trials with Omega 3

COMPLETED:

• 240mg/ day DHA + ARA improved memory and attention in amnestic MCI (but not AD)- Japan - Kotani et al 2006
• Completed 4 gm fish oil (1.7 gm DHA), MMSE> 27 pos. stabilized ( but not in AD) -Sweden- Freund-Levi et al 2007
• Memo trial -n=302 65+ yrs, cognitively healthy (1800 or 400 mg EPA+DHA for 26 wks)- increases in attention,especially in E4 and men, but no change in cognition (Holland)
• Fish oil plus 600mg alpha lipoate improved MMSE in AD (Oregon- L. Shinto et al 2008 abstract report- OHSU)-
• Fish oil (1.8 gm omega 3) improved ADAScog (p=0.03) over olive oil placebo in MCI but not AD ( n=23) -Taiwan- Chiu et al 2008

ONGOING:

• MIDAS ( US -Yurko-Mauro, Martek 900 mg DHA)- Early memory deficits
• ADCS 2 gm DHA/day mild to mod AD (Quinn- US)
• Primary Prevention ( B. Vellas South of France)
• Opal trial -500 mg DHA + 200 mg EPA (n=800, A. Dangour, UK)-
ApoE4 accelerates age of onset

- E4 accounts for 90% of the new AD cases until 80 years of age (Raber et al 2004). F Gender.
- No impact on rate of clinical progression (?)
Omega-3/ fatty fish protection only w/o ApoE4 in 3 studies

1) Huang, TL et al. 2005 Neurology Cardiovascular Health Cognition Study-USA Reduced risk for AD only w/o E4.

2) Barberger-Gateau, P et al 2007 Neurology Three-City Cohort Study, France Reduced risk of dementia and AD only w/o E4.

3) Whalley, LJ et al 2008 Am J Clin Nutr. Reduced cognitive decline only in normal older non-E4 cohort (Aberdeen, UK)
Pre-specified sub-group analyses:
ADCS result in ApoE4 positive and negative subjects

E4 positive (57.7%)
n=137 DHA; n= 95 placebo

E4 negative (42.3%)
n=91 DHA; n=67 placebo

*p<0.028*

*not corrected for multiple comparisons*

E4 vs E3 impact on Aβ accumulation reversed on high LA diet: LA reduced, DHA increased plaques!

Diet - PMI 5015

Treat Cont 2x LA +/- DHA from 2-3 to 8-9 mos.
JNK Inhibitor or DHA blocks AβO-induced pIRS-1 and ptau

Fig 3. JNK inhibitor blocked Aβ oligomer-induced IRS-1pS616 and taupS422 phosphorylation.

Fig 4. DHA prevented Aβ oligomer-induced IRS-1 and tau phosphorylation.
DHA only reduced pJNK in ApoE3FAD (not ApoE4FAD)

Fig 4. DHA prevented Aβ oligomer-induced IRS-1 and tau phosphorylation.
DHA increased CRP in 3/4 people

APOE genotype influences triglyceride and C-reactive protein responses to altered dietary fat intake in UK adults\(^1\)\(^-\)\(^3\)

Andrew L Carvalho-Wells, Kim G Jackson, Stacey Lockyer, Julie A Lovegrove, and Anne M Minihane


- 8 wks on Low (LF) or High saturated fat (HSF) diets or HSF + DHA (3.45 g/d)
- Open squares E3/3 (n=44)
- Black squared E3/4 (n=44)
- DHA reduced plasma Tgs in 3/3 and 3/4 but inflammation (CRP) only in 3/3 not E3/4
EFAD+ mice have motor defects with age > 50% mortality with DHA alone in E4FAD+. DHA + curcumin treats...
Neuron loss causes dementia? Stem cells to treat?

Born with 100 Billion Neurons
Living/Learning/Training/Studying---Neurons form Networks

Neurons loss causes network deficiency leading to memory loss, other cognitive deficits and behavior changes.
Although the boy had an IQ of 126 and had a first class honours degree in mathematics, he had "virtually no brain". A CAT scan showed a thin layer of brain cells to a millimeter in thickness, the rest was cerebrospinal fluid. The young man continues a normal life with the exception of his knowledge that he has no brain...

"I can't say whether the mathematics student has a brain weighing 50 grams or 150 grams, but it is clear that it is nowhere near the normal 1.5 kilograms." - Dr J. Lorber, Neurologist
Dendritic Arbor, Spine & Synapse loss

MOOLMAN, SHELANSKI-04
LOSS OF DREBRIN OCCURS EARLY AND CORRELATES WITH MMSE- COUNTS ET AL 2006
APP TG models with plaques but no tangles have limited neuron & synaptophysin loss

On diets with low $\omega$-6/$\omega$-3 ratios
BAD Diet depleted of DHA(\(\omega 3\))

Calon et al Neuron Sept 2004

- Tg2576 + and Tg- Mice aged to 17 months on standard (Purina 5015) breeder chow diet (\(\omega-6/\omega-3 \sim 7:1\))
- From 17 to 22.5 months, groups placed on 3 different diets:
  1. Standard diet (\(\omega-6/\omega-3 = 7:1\))-soy
  2. BAD diet (\(\omega-6/\omega-3 = 85:1\))-safflower
  3. BAD diet + DHA (\(\omega-6/\omega-3 = 8:1\)).
Tg+: DHA depletion > KO of drebrin, low PSD-95 & high caspase activation

- Standard Diet
- Low DHA Diet
- High DHA Diet

% of Std Diet Fed Tg- mice

Drebrin

PSD95

Fractin/actin

††† p < 0.001 vs. Standard diet

○○○ p < 0.001 vs. Low DHA diet
JNK Inhibitor or DHA blocks AβO-induced pIRS-1 and ptau

Fig 3. JNK inhibitor blocked Aβ oligomer-induced IRS-1pS616 and TaupS422 phosphorylation.

Fig 4. DHA prevented Aβ oligomer-induced IRS-1 and tau phosphorylation.
IRS-1 phosphorylation by JNK, GSK3 uncouple IRS-1 causing insulin/ neurotrophic factor “resistance”
Cytosolic P-IRS-1 (s312, 616) is increased and IRS-1 lost in AD

- P-IRS-1 labels some plaque neurites and tangles in AD brain
- (confirms K. Talbot et al Abs 03-02-02 at ICAD/ SFN 07 who showed progressive increase from MCI to AD) ; also Moloney et al NBA 2008

IRS-1 and pAkt cytosol are lost
DHA Limits AD-like pIRS-1 defect

Tg2576
17-22 mos +/- DHA:
No intraneuronal Aβ or tangles

IRS-1 pSer312 in Nuclear Fraction-Westerns
APP Tg+ suppresses and DHA protects Akt inhibitory control of GSK3β

• Active GSK drives tau pathology and abeta toxicity (Takashima et al 1994)
DHA from 17 mos lowers plaque burden in 22 mo Tg2576

Lim et al 2005 Jnsci.
DHA Reduced Insoluble Aβ (trial 2); 4 studies confirm, and DHA Reduces Aβ From Human Neurons In Vitro-Bazan

- DHA reduced Aβ accumulation in aged 17-22 mo Tg2576- trial 2, n-6/n-3 ~40/1 repeating
  Lim et al. J Neurosci. 2005

- Oksman et al, Tanila et al, Green et al, Mufson (But not Arendash) confirm Aβ reduction in vivo

- 500nM DHA reduces abeta production from human neurons in vitro
Proposed Mechanisms for DHA

- Anti-inflammatory (+PPARg, reduces AA, PGE2)
- Neuroprotective - precursor to anti-apoptotic NPD1 (Bazan);
- Increases antioxidant defense enzymes
- Increases abeta chaperone (TTR-Goldgaber)
- Increases SorLA/LR11 that limits Aβ production
- Reduces PS1 (Green...LaFerla). Fluidity
- Promotes neurotrophic Akt (Akbar & Kim)
- Suppresses major tau kinases GSK3β, JNK
- Reduces IRS-1 inactivation implicated in Type II diabetes (“insulin/trophic factor resistance”)
- Increases BDNF (Rapoport, Gomez-Pinilla)
How could DHA reduce AD risk?

Inhibition of tangle formation via inhibition of

- Inflammation > tau kinases
- GSK3β > ptau, JNK > ptau (also pIRS-1 and neurotrophic resistance)
- Caspase activation
- Aβ production

Inhibition of amyloid peptide (Aβ) production

- Increasing membrane fluidity (in opposition to cholesterol, reducing cholesterol) and altering APP metabolism
- Increasing SorLA/LR11 or reducing g-secretase activity to reduce Aβ production
- Miscellaneous Improvements in:
  - Coupling blood flow to glucose utilization
  - G protein coupling
  - Cholingeric neurotransmission
  - K+ channel and GABA effects

Trophic factors (reported elevations in BDNF, NGF and GDNF)
Conclusions

- DHA has multiple mechanisms of action including reducing AA and metabolites and increasing NPD1
- Limiting pJNK and pIRS-1 defects from AβO in vitro and in vivo to correct PI3-k>Akt> GSK3
- JNK is a priming kinase for GSK3 phosphorylation of both IRS-1 and tau
- DHA / omega 3 work better combined with antioxidants and/or NSAIDs (curcumin)
- Clinical trials, epidemiology suggest less efficacy with ApoE4 (without antioxidants/ NSAIDs or exercise).
- Omega 3 have been shown to be protective in CVD and CVD accelerates dementia
Fish for dinner.
Maybe curry for lunch.
Lab
Qiulan Ma, MD, PhD
Fusheng Yang, MD
Atul Deshpande, PhD
P.P. Chen
Walter Beech
Oliver Ubeda

Former lab
Frederic Calon, PhD
Giselle Lim, PhD
Lixia Zhao, PhD
Takashi Morihara MD, PhD
Sheldon Ball, MD, PhD
Emily Rosario, PhD

Sally Frautschy
K. Hsiao Ashe-Tg2576
N. Salem
Edmond Teng, MD, PhD

Support : NIA, NCAM
w-3 Fatty Acid Treatment in 174 Patients With Mild to Moderate Alzheimer Disease: OmegAD Study: A Randomized Double-blind Trial

Freund-Levi... Palmblad Arch Neurol. 2006;63:1402-1408

1.7 g/day DHA in fish oil for 6 mos

Negative except MMSE 27+

(possible arrest in decline)
DHA’s Multiple Mechanisms
Insulin protects pPAK, drebrin from Aβ oligomers

Zhao et al
SFN-04
Aβn>FYN>TIAM1>RAC>PAK>LIM K1> COFILIN>synaptic deficits

Omega-3 DHA Or curcumin Protect In vitro And In vivo

Ma et al JBC 2008
Impact of different saturated fatty acid, polyunsaturated fatty acid and cholesterol containing diets on beta-amyloid accumulation in APP/PS1 transgenic mice

- Oksman… Tanila. NBD 2006
- Reduced Aβ production, but not plaques

Hippo
Aβ
6-10m
Control Risk Factors for CVD & Dementia for Preventing Dementing

**Increase risk**
- Low exercise
- High cholesterol, low HDL
- Type II diabetes
- High saturated fat
- Inflammation-CRP
- Low fish/DHA
- High blood pressure
- High homocysteine

**Protection**
- Exercise (walk >2 miles/day)
- Statins-Lipitor trial positive
- Folate?
- High Fish/DHA, low sat fat
- Vit E/Vit C+ ibuprofen
- Curcumin
- Polyphenols-High Fruits? & Veggies, Juices?
- Red wine & modest alcohol
Curcumin & DHA reduced drebrin & postsynaptic marker loss in vivo in Tg2576

<table>
<thead>
<tr>
<th>Diet (all Tg+)</th>
<th>Synaptopophysin</th>
<th>Drebrin</th>
<th>PSD-95</th>
<th>CaMK II</th>
</tr>
</thead>
<tbody>
<tr>
<td>STD</td>
<td>22.93</td>
<td>3.84</td>
<td>8.79</td>
<td>9.12</td>
</tr>
<tr>
<td>Bad</td>
<td>22.9</td>
<td>0.6</td>
<td>3.5</td>
<td>0.97</td>
</tr>
<tr>
<td>Bad +CUR</td>
<td>26.50</td>
<td>3.87</td>
<td>4.94</td>
<td>7.34</td>
</tr>
<tr>
<td>Bad+CUR+DHA</td>
<td>26.21</td>
<td>4.79</td>
<td>5.67</td>
<td>8.82</td>
</tr>
</tbody>
</table>
Diet and Tg Reduce NMDA and CamKII- Partial DHA protection

Table 3 - Synaptic markers in the cortex of Tg(-) mice

<table>
<thead>
<tr>
<th>Tg(-)</th>
<th>N</th>
<th>NR2A</th>
<th>NR2B</th>
<th>NR1</th>
<th>Synaptophysin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>13</td>
<td>100 ± 3</td>
<td>100 ± 20</td>
<td>100 ± 11</td>
<td>100 ± 7</td>
</tr>
<tr>
<td>Low n-3 PFA</td>
<td>6</td>
<td>47 ± 7† †</td>
<td>37 ± 10† †</td>
<td>97 ± 10</td>
<td>98 ± 2</td>
</tr>
<tr>
<td>Low n-3 PFA + DHA</td>
<td>7</td>
<td>58 ± 13†</td>
<td>53 ± 19† †</td>
<td>73 ± 15</td>
<td>101 ± 3</td>
</tr>
</tbody>
</table>

Figure 1

Figure 2

VERY LITTLE DHA EFFECT ON NR2A/ B

CALON ET AL EJN 2005
Dendritic Arbor, Spine & Synapse loss

MOOLMAN, SHELANSKI-04
Tg X diet from 17-22 mos depletes excitatory synapse marker, PSD-95

Calon et al 2004, Neuron

Tg^−

Tg^+

% of standard diet fed Tg^- mice

% of standard diet fed Tg^+ mice

††† p < 0.001 vs Standard diet

°°° p < 0.001 vs Low DHA diet

Also High DHA- Improved Cognitive function

Standard Diet

Low DHA Diet

High DHA Diet

Calon et al 2004, Neuron

High DHA-

Improved

Cognitive

function
Omega-3 Fatty Acids and Lipoic Acid in Alzheimer’s Disease- Shinto et al-08

Neurology vol 70(11) Supplement 1: A393 2008

• 3 groups, randomized, double-blind, 1 yr, placebo-control trial, \geq 55\ yrs., probable AD (MMSE 15-26) :
  • 1. placebo,
  • 2. omega-3 ( 3 gms fish oil = 675 mg DHA, 975 mgs EPA, Nordic)
  • 3. omega-3 plus 600 mg Lipoate.
• Results MMSE UP with group 3 ( p=0.02)
• Activities daily living improved in both omega -3 groups ( p=0.005) ( RBC DHA`7-8%)
DHA suppresses Aβn-induced loss of NR2B/pNR2B and Tiam1/rac/Pak (translocation) in primary neurons

Fig 1. DHA protected from Aβ oligomer-induced NR2B loss in cultured primary neurons.

Fig 2. DHA protected Aβ oligomer-induced reduction of Tiam1 in primary neurons.

Fig 3. DHA prevented Aβ oligomer-induced pPAK loss in cultured primary neurons.

Fig 4. DHA protected Aβ oligomer-induced reduction of pRac in primary neurons.

NMDA/ Tiam1/ Rac/Pak protected
CAN NSAIDS REALLY BE USED FOR PREVENTION?
VA Epidemiology-08

- Protective effects of NSAIDs on the development of Alzheimer disease
  - Vlad et al Neurology 2008;70;1672-1677

- ADAPT CLINICAL TRIAL-2,528 subjects
  - 2001-2004 halted
  - Dec 17, 2004 (Vioxx news)
  - >2,000 in follow-up 2007

Prevention trial- Breitner et al unpublished 08
Nuclear P-IRS-1 (s312) is lost while cytosolic is increased in 3xAD- Tg mice

- P-IRS-1 (green) colocalizes (yellow) with some ptau PHF-1 (red) in older 3xTg
- Progressive increase in cytosolic P-IRS-1 (s312) in cytosol which overlaps ptau by 7-8 mo with nuclear loss by 18 mo
Increased cytosolic p-IRS-1 in 6 mo 5xFAD mouse CA1 (Vassar)

- Increased p-IRS-1 in cytosol and neurites
- Partial overlap of intraneuronal abeta, but doesn’t require mutant human tau/ tangles suggesting an Aβ mediated defect
SorL1 is a new AD gene whose Aβ-reducing product LR11 is lost in neurons in LOAD.

The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease.


LR11 down 25% in AD

A: CA1–CA3 pyramidal neurons
B: dentate granule cells
C: frontal cortex pyramidal neurons
D: Purkinje cells of the cerebellum

DHA in vitro or Chronic DHA in diet increases LR11 in the the brain

Ma et al. J. Neurosci. 07

- aged DHA-depleted mice (17-22 mo) fed diet w/o DHA (BAD) or + 0.6% DHA
- In young diabetic rats on a high fructose diet fed 2% fish oil
- Also in 3xTg AD mice fed 2.3% fish oil from 5 to 9 months (unpublished)
IRS-1 is an adaptor protein coupling insulin and neurotrophic factor receptors to PI3-K> Akt

- IRS-1 is inactivated by hyperphosphorylation at serine/threonine residues resulting in uncoupling from membrane bound receptors and a shift to cytosolic compartments.
- Like tau, multiple kinases can ser/threonine phosphorylate IRS-1 and like tau, major IRS kinases are JNK and GSK3β.
- Hypothesis: uncontrolled activation of JNK and GSK3 in AD brain/tangle bearing neurons inactivates and uncouples IRS-1 leading to insulin/neurotrophic factor “resistance” and plasticity defects.
Ins / Neurotrophic Factors

IRS-1 phosphorylation by JNK, GSK3 uncouple IRS-1 causing insulin/ neurotrophic factor “resistance” - DHA limits this
APP Tg causes major loss of pERK & pCREB but DHA fails to protect

- pERK > pCREB promotes LTP & learning and memory in multiple models, including APP Tg
Dendritic Arbor, Spine & Synapse loss

MOOLMAN, SHELANSKI-04
DHA reduces AA & metabolites

M. Strokin, M. Sergeeva and G. Reiser
Prostaglandin synthesis in rat brain astrocytes is under the control of the n-3 docosahexaenoic acid, released by group VIA calcium-independent phospholipase A2. J. Neurochem., 2007, 102, 1771–1782

D. Cao, C. Zhou, L. Sun, R. Xue, J. Xu, Z. Liu
### Table 1: Effect of DHA on AA Levels

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>20:4n-6</th>
<th>22:4n-6</th>
<th>22:6n-3</th>
<th>n-6/n-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tg(-)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>13</td>
<td>9.6 ± 0.1</td>
<td>2.83 ± 0.07</td>
<td>19.2 ± 0.3</td>
<td>0.70 ± 0.01</td>
</tr>
<tr>
<td>Low n-3 PFA</td>
<td>6</td>
<td>9.8 ± 0.1</td>
<td>3.00 ± 0.12</td>
<td>18.0 ± 0.5</td>
<td>0.84 ± 0.02**</td>
</tr>
<tr>
<td>Low n-3 PFA + DHA</td>
<td>7</td>
<td>8.4 ± 0.2</td>
<td>2.13 ± 0.10</td>
<td>20.5 ± 0.5</td>
<td>0.57 ± 0.02</td>
</tr>
<tr>
<td>Tg(+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>8</td>
<td>9.5 ± 0.1</td>
<td>2.62 ± 0.08</td>
<td>19.5 ± 0.5</td>
<td>0.69 ± 0.02</td>
</tr>
<tr>
<td>Low n-3 PFA</td>
<td>6</td>
<td>9.9 ± 0.2</td>
<td>3.01 ± 0.12**</td>
<td>16.4 ± 0.8**_à</td>
<td>0.96 ± 0.06**_à</td>
</tr>
<tr>
<td>Low n-3 PFA + DHA</td>
<td>6</td>
<td>7.9 ± 0.2*</td>
<td>1.89 ± 0.12</td>
<td>21.3 ± 0.6</td>
<td>0.51 ± 0.02</td>
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</tbody>
</table>