High Dose DHA supplementation in APOE4 carriers

ADC Clinical Cores
Datablitz 2018

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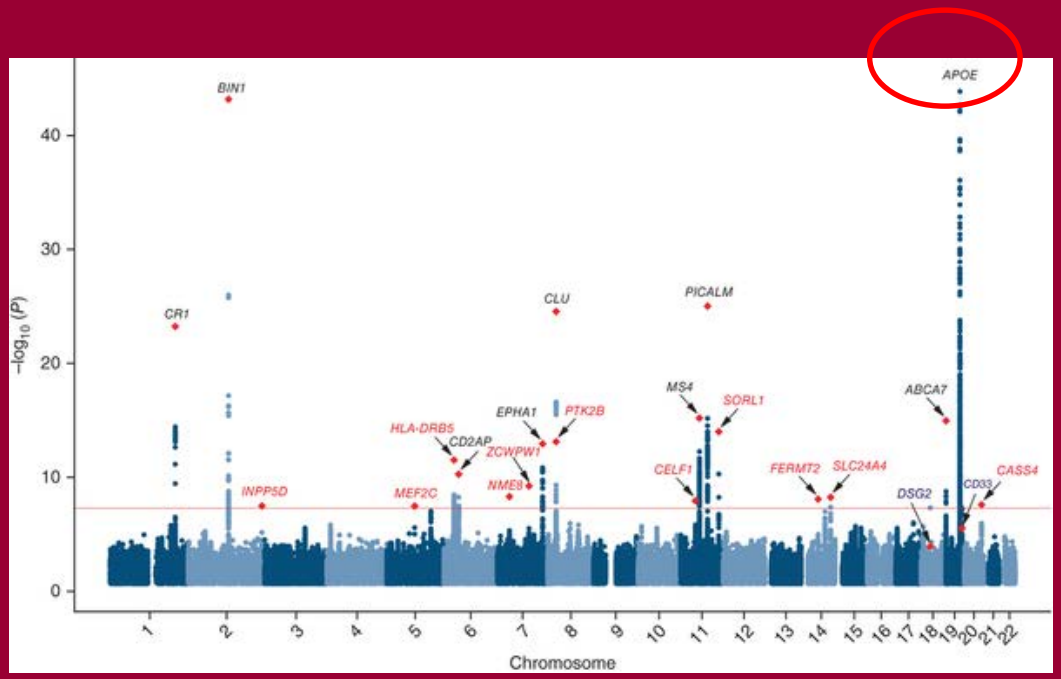
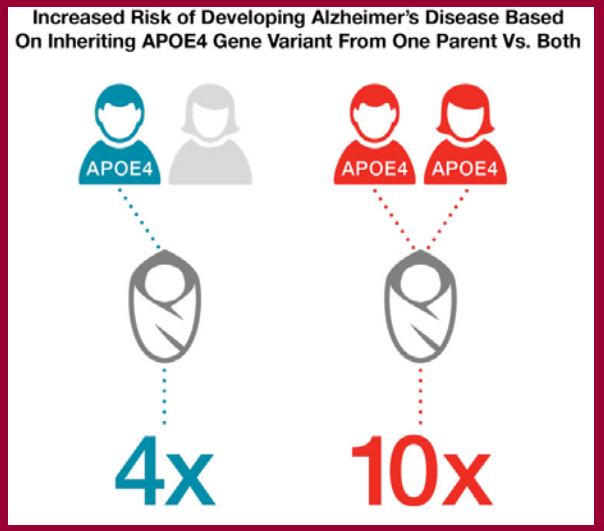
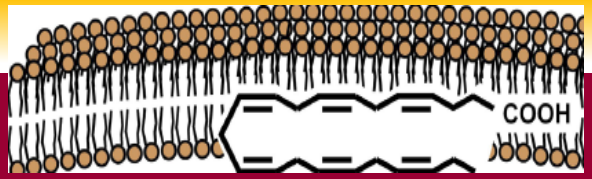
APOE ε4 strongest genetic risk factor for late onset AD





Lambert et al Nature Genetics 2013

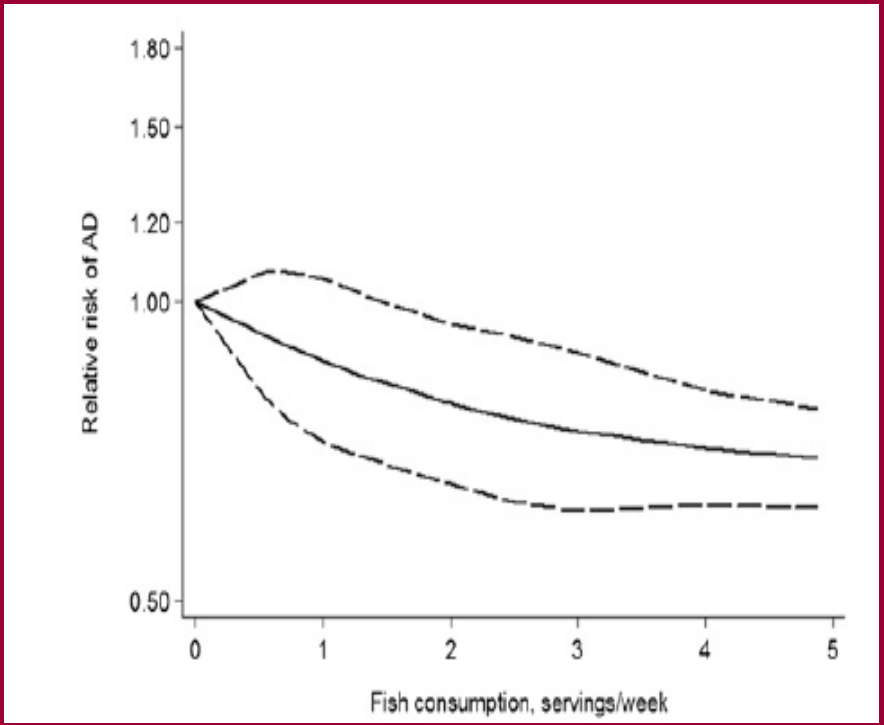
Docosahexaenoic acid (DHA)



- DHA (22:6n-3), a polyunsaturated fatty acid
- Makes up to 40% of fatty acids in grey matter
- Mainly obtained from fish consumption
- In APOE4 AD animal models, high dose DHA supplementation prevents AD phenotype
- Depleted in phospholipids of AD brains
- Clinical trials of DHA in patients with AD were negative

Söderberg Lipids, 1991

Fish consumption is associated with decreased risk of AD: Meta-analysis of 21 epidemiology studies (n=181,580)

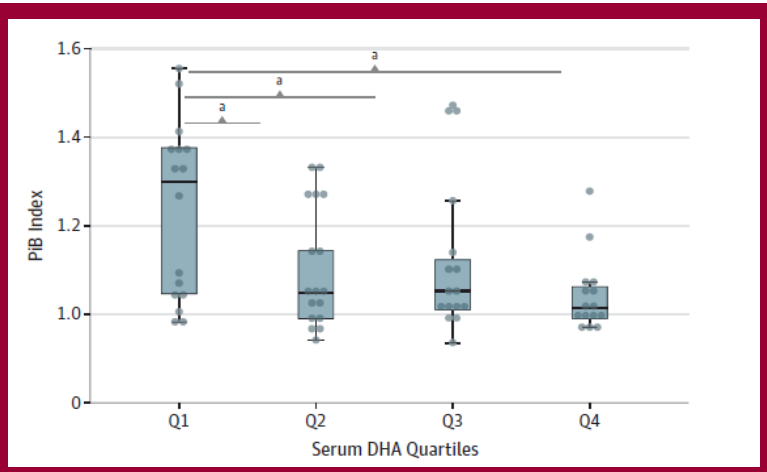


- 21 omega-3 studies
- 181,580 participants
- 4438 cases during 2.1 - 21 yr follow-up
- One-serving/wk of fish was associated with lower risk of AD dementia
- RR: 0.93; 95% CI: 0.90, 0.95; P =0.003

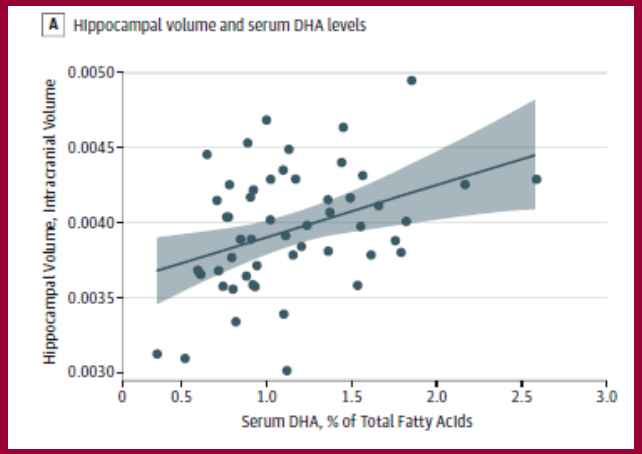
Zhang at al AJCN, 2016

Serum DHA levels are inversely correlated with cerebral amyloidosis in older adults without dementia but not in patients with AD (Collaboration with the Aging Brain Study, n=61)

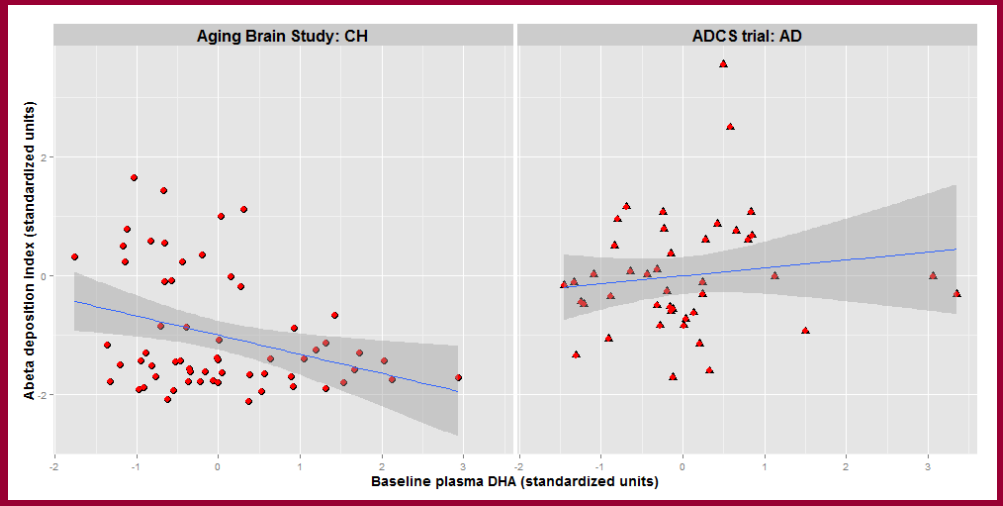
Amyloid deposition index



Hippocampal volume



Yassine et al, JAMA Neurol 2016

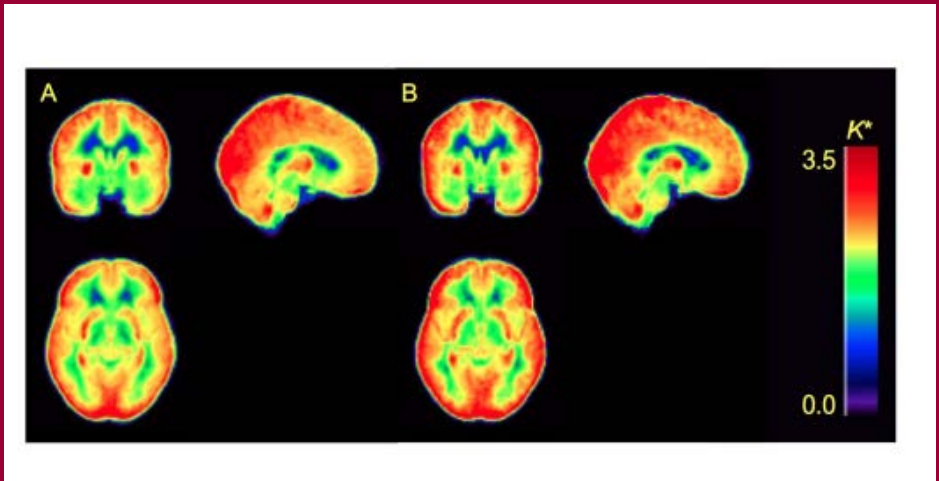


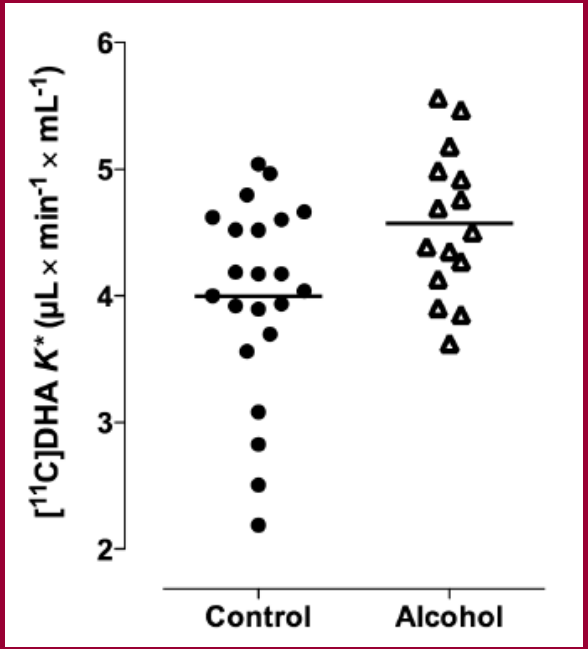
These findings suggest a role for DHA in the prevention rather than the treatment of AD

Effect of APOE4 on DHA brain transport in younger cognitively healthy adults

[^{11}C] DHA PET can be used to study brain DHA metabolism

IV [^{11}C] DHA followed by determination of brain DHA uptake from plasma





Alcohol withdrawal associates with an increased brain DHA uptake

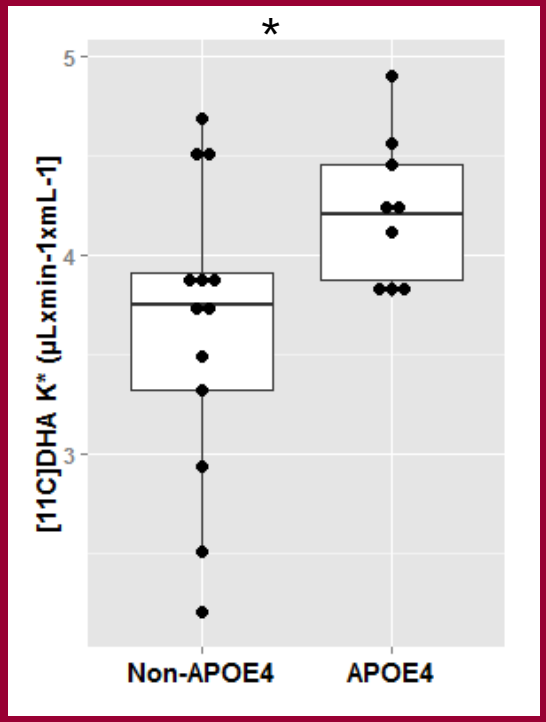
Umhau et al PLOS one 2013

Collaboration with Stanley Rapoport and John Umhau, NIA

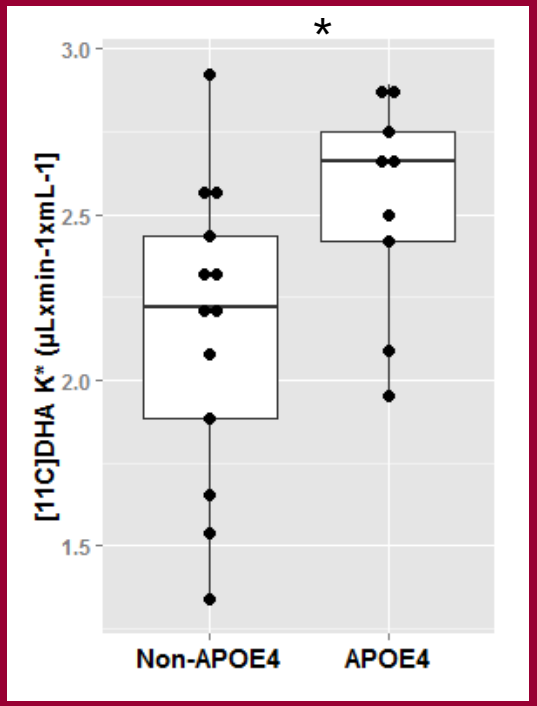
ApoE4 and brain DHA metabolism

- Hypothesis: APOE4 associated with brain DHA deficit
  - i.e., increased plasma to brain DHA ratio
- Investigated effect of APOE4 on [1-^{11}C]-DHA brain kinetics in healthy adults
  - 13 non-carriers and 9 APOE4 carriers
  - average age 37

Greater plasma to brain DHA uptake in global gray matter areas and particularly in the medial temporal lobe in cognitively non-impaired APOE4 carriers compared with non-carriers



Global gray matter brain K* for DHA.



Medial temporal lobe K* for DHA.

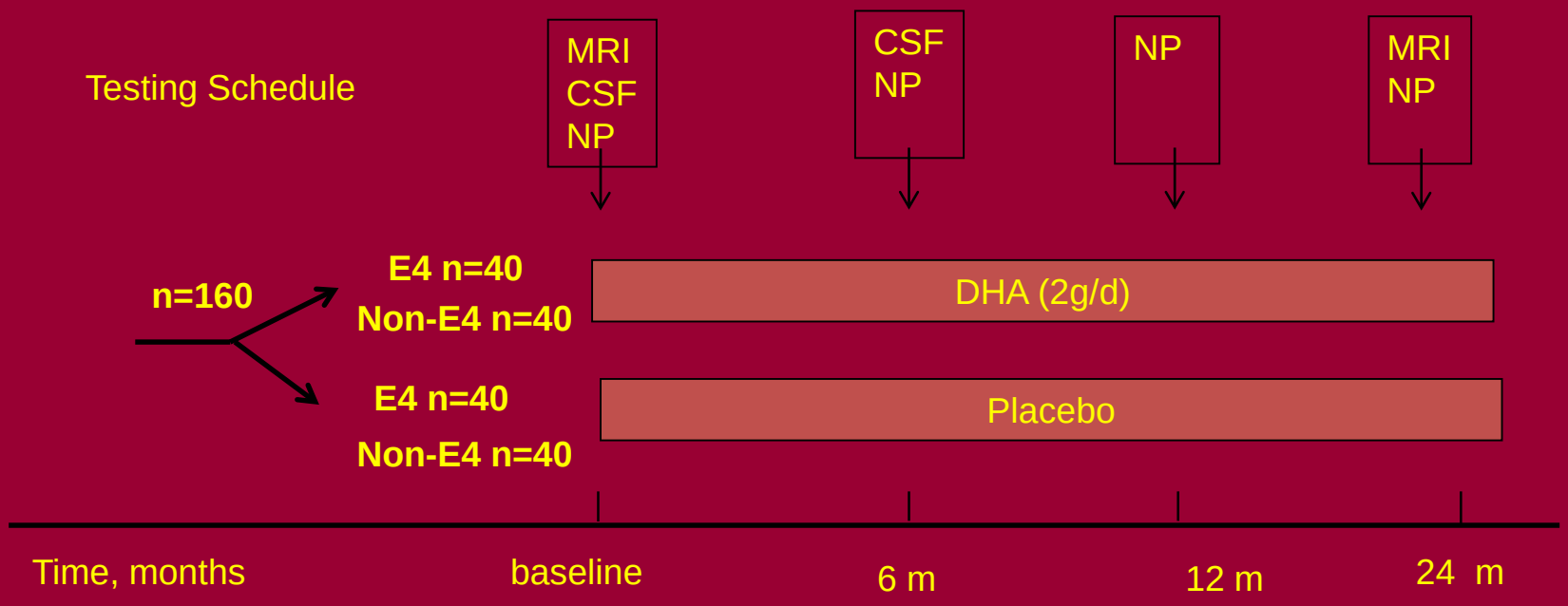
The greatest uptake for DHA was in the entorhinal brain area

Yassine et al. Alz Research and Therapy 2017

Summary

- Lower serum DHA levels associate with increased brain amyloidosis in older patients without dementia, but not in patients with dementia
- ApoE4 is associated with an increased brain uptake of [^{11}C] DHA from plasma in brain regions that coincide with areas affected by AD pathology. This suggest the APOE4 brain is vulnerable to DHA deficiency
- There is a window for a therapeutic opportunity by supplementing cognitively normal APOE4 carriers with low DHA consumption with high dose DHA supplementation before the onset of dementia

DHA Brain Delivery Trial



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