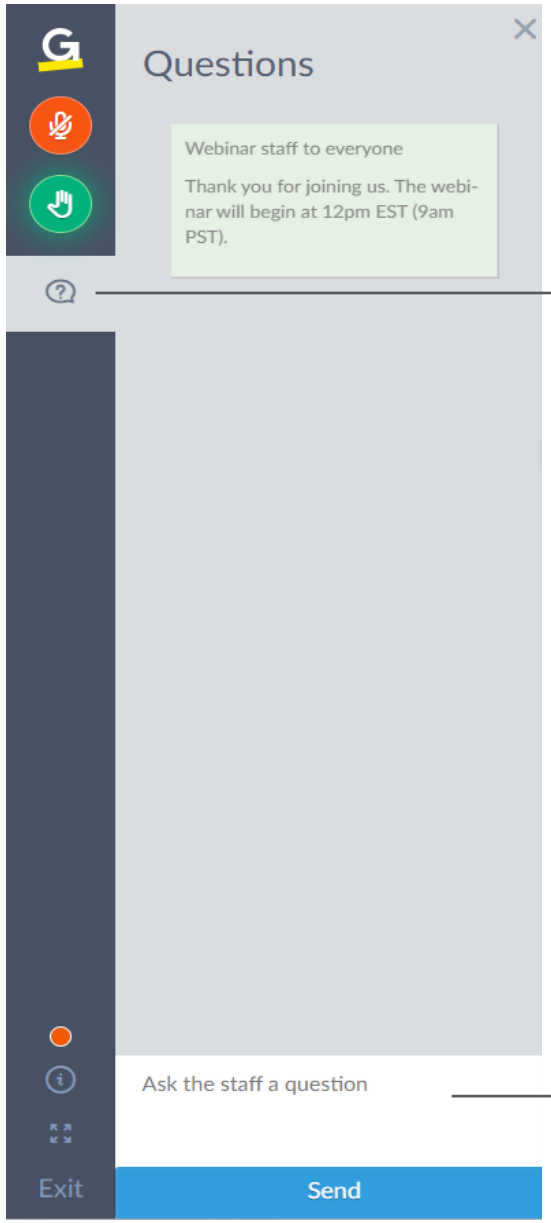
MoCA COGNITION

MoCA Talk #13: The Effect of the APoE4 Gene on Neurocognitive Decline and Possible Mitigating Interventions

Anne Marie Minihane, Phd,
Professor Of Nutrigenetics



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Featured Speaker

Anne Marie Minihane, Phd,
Professor Of Nutrigenetics

- Investigates the impact of dietary components and HRT on cognitive health and dementia risk
- Focuses on molecular & physiological basis for interactive impact of menopause & APOE4 genotype on health outcomes
- Leads Norwich Institute of Healthy Ageing (NIHA)

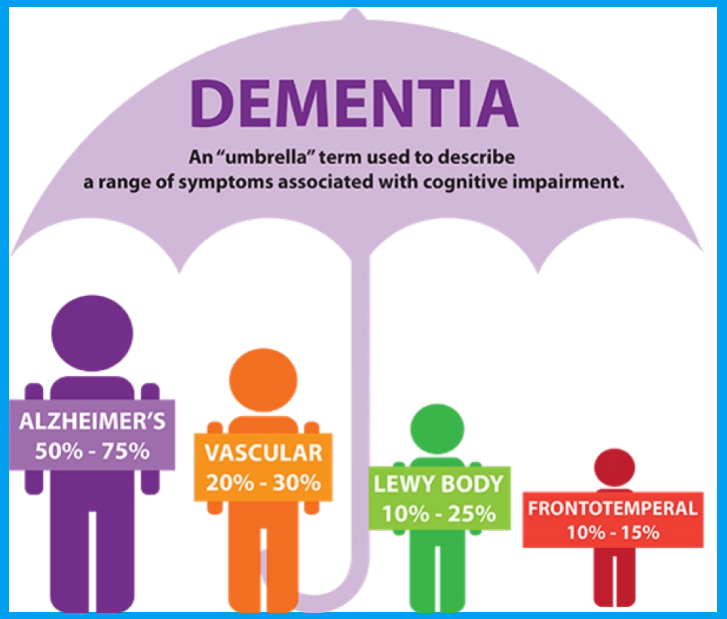
The Effect of the APoE4 Gene on Neurocognitive Decline and Possible Mitigating Interventions

Anne-Marie Minihane

Nutrition and Preventive Medicine

University of East Anglia | Norwich Medical School

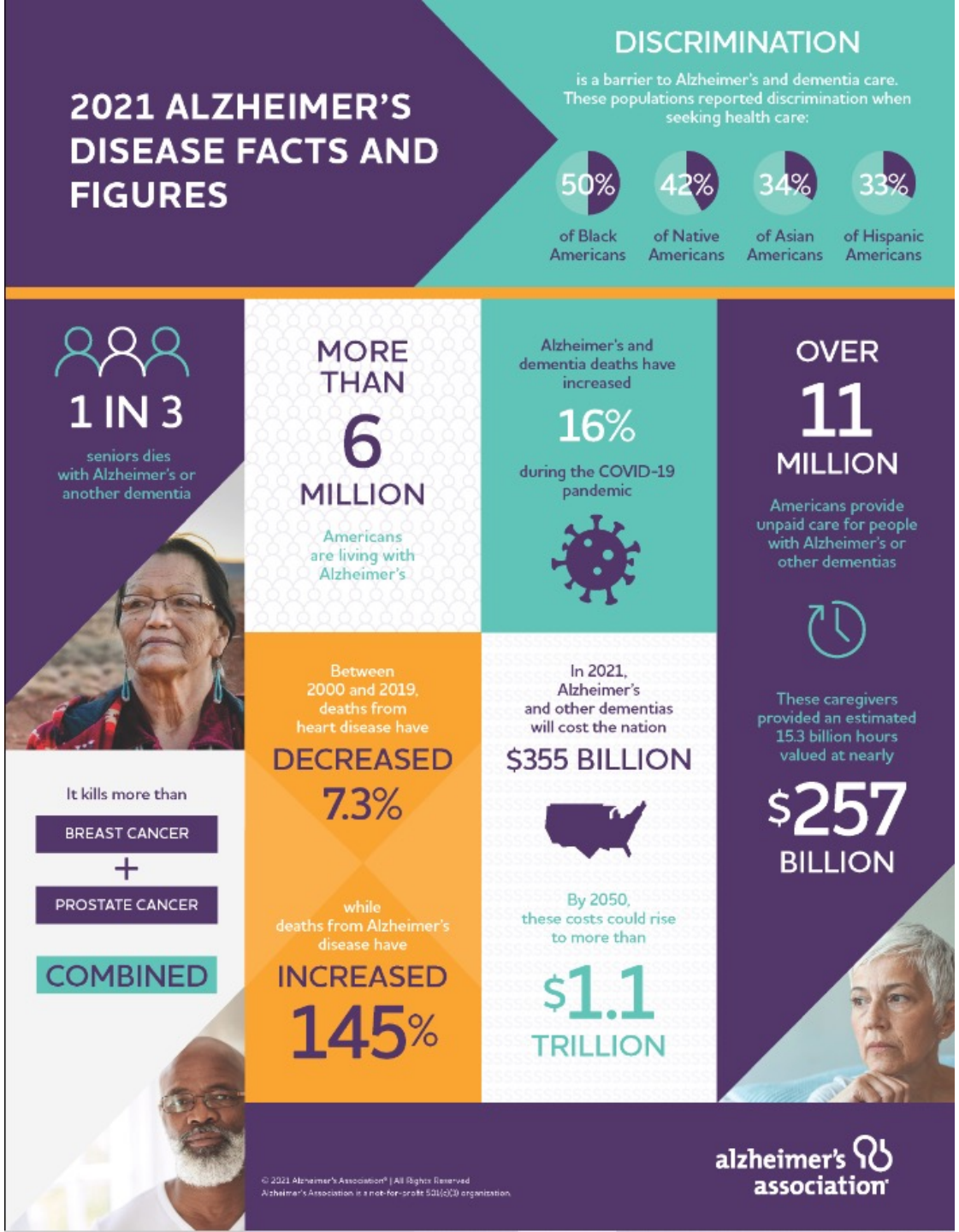
Athena SWAN Silver Award



- 944,000 cases UK

- 16.5% of mortality women
- 8.7% of mortality men

- 1/14 over 65y
- 1/6 over 80y



Poll 1

Source: Prince, M et al (2014) Dementia UK: Update Second Edition report produced by King's College London and the London School of Economics for the Alzheimer's Society

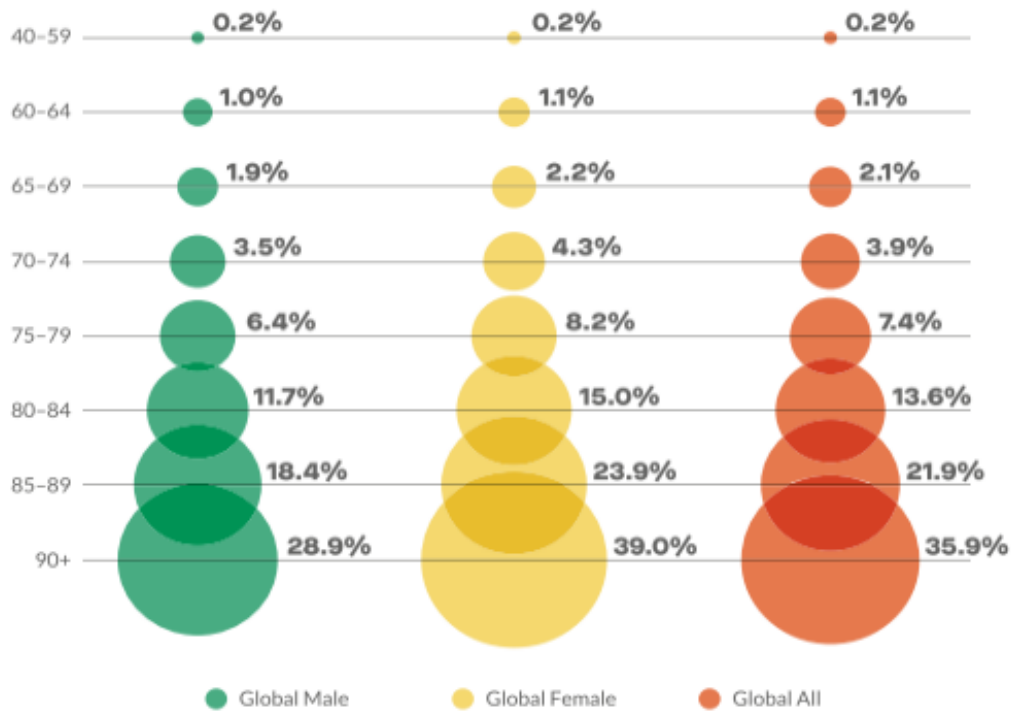
Source: Prince, M et al (2014) Dementia UK: Update Second Edition report produced by King's College London and the London School of Economics for the Alzheimer's Society

Dementia…..

- **Higher age-standardised prevalence in women**

FIGURE 2

Global dementia prevalence rates by sex and age



(WHO, 2021)

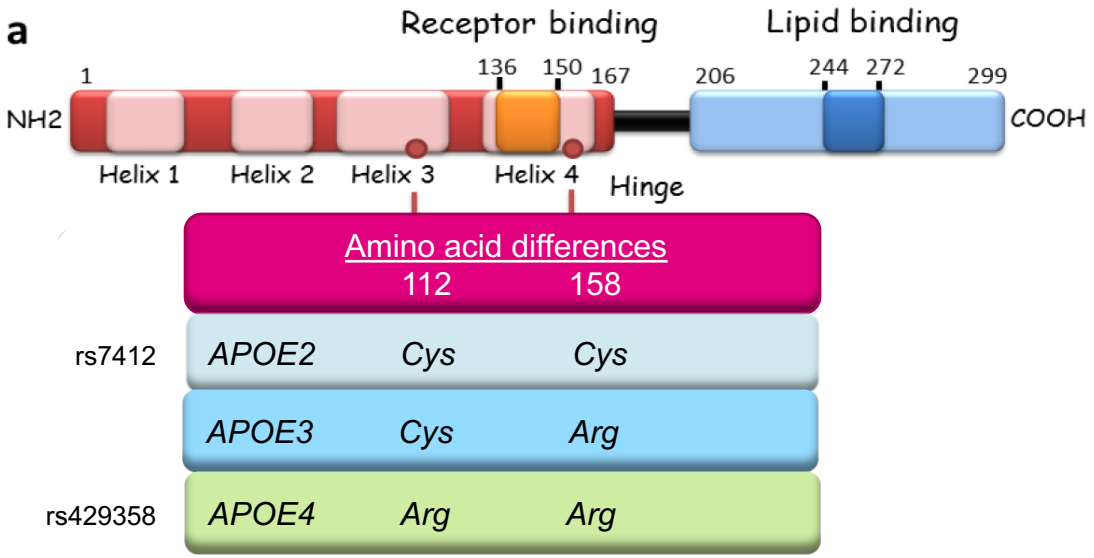
- Higher age-standardised rates in females likely to in part due to the greater penetrance of the *APOE4* genotype

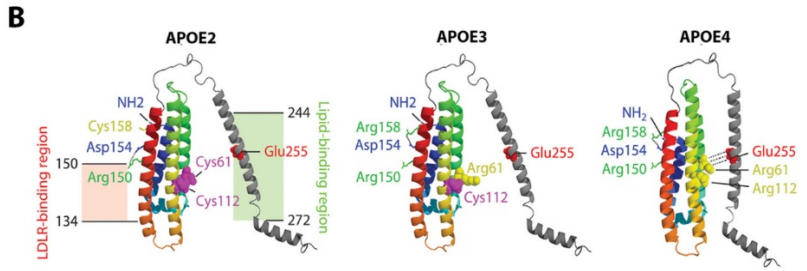
- *APOE4* is the most important common genetic determinant of cognitive decline and dementia risk

- Predictive not prognostic

APOE genotype explained

Liver (80-90%), brain and macrophages





E2/E2	E2/E3	E2/E4	E3/E3	E3/E4	E4/E4
1%	12%	2%	63%	20%	2%

APOE genotype and longevity

- *APOE4* is associated with reduced longevity and is termed a ‘frailty’ genotype

Published in final edited form as:
Aging Cell. 2013 April ; 12(2): 184–193. doi:10.1111/acel.12039.

Genome-wide linkage analysis for human longevity: Genetics of Healthy Ageing Study

Marian Beekman[1,2,*], Hélène Blanché[3], Markus Perola[4], Anti Hervonen[5], Vladyslav Bezrukov[6], Ewa Sikora[7], Frederieke Flachsbart[8], Lene Christiansen[9], Anton J.M. De Craen[10,2], Tom B.L. Kirkwood[11], I. Meave Rea[12], Michel Poulain[13,14], Jean-Marie Robine[15], <recruitment Bologna>[16], Maria Antonietta Stazi[17], Giuseppe Passarino[18], Luca Deiana[19], Efstathios S. Gonos[20], Silvana Valensin[16], Lavinia Paternoster[21,22], Thorkild I.A. Sørensen[23,24], Qihua Tan[9,25], Quinta Helmer[26], Erik B. Van den Akker[1,27], Joris Deelen[1], Francesca Martella[26,28], Heather J. Cordell[11], Kristin L. Ayers[11], James W. Vaupel[29], Outi Törnwall[4], Thomas E. Johnson[29], Stefan Schreiber[8], Mark Lathrop[3], Axel Skytthe[9], Rudi G.J. Westendorp[10], Kaare Christensen[9,25], Jutta Gampe[30], Almut Nebel[9], Jeanine J. Houwing-Duistermaat[26,2], P. Eline Slagboom[1,2,31], and Claudio Franceschi[16,31] on behalf of On behalf of the GEHA consortium

- *APOE4* allele frequency nonagenarians 6.8% vs. 12.7% in matched controls (55-75y)
- OR to become a nonagenarian 0.48 (95% CI 0.42-0.55) in *APOE4* vs non-*APOE4*

APOE genotype and Alzheimer's Disease (AD)

Table 1 Association of APOE genotypes and allelic doses compared to the APOE3/3 genotype.

APOE	Neuropathologically confirmed group			Neuropathologically unconfirmed group		
	OR	95% CI	*P*	OR	95% CI	*P*
Genotype						
2/2	0.13	0.05–0.36	6.3×10^{-5}	0.52	0.30–0.90	0.02
2/3	0.39	0.30–0.50	1.6×10^{-12}	0.63	0.53–0.75	2.2×10^{-7}
2/4	2.68	1.65 4.36	7.5×10^{-5}	2.47	2.02 3.01	5.7×10^{-19}
3/4	6.13	5.08–7.41	2.2×10^{-75}	3.55	3.17–3.98	2.3×10^{-105}
4/4	31.22	16.59–58.75	4.9×10^{-26}	10.70	9.12–12.56	7.5×10^{-186}
Allelic dose						
2	0.38	0.30–0.48	1.1×10^{-15}	0.64	0.58–0.72	2.2×10^{-16}
4	6.00	5.06–7.12	3.4×10^{-90}	3.43	3.26–3.60	$<10^{-300}$

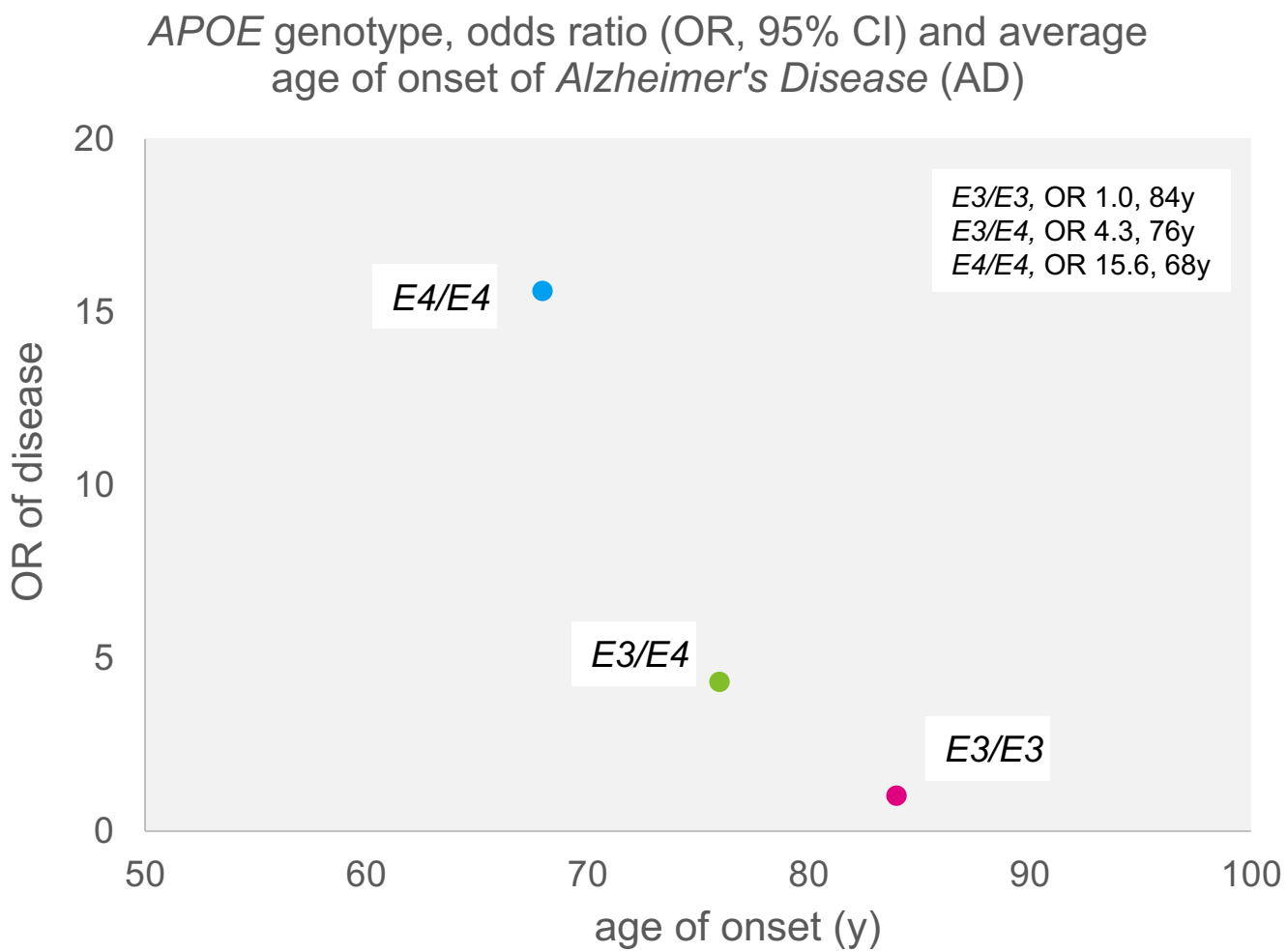
For genotypic association tests, odds ratio (OR), 95% confidence interval (CI), and *P* value (*P*) for each APOE genotype compared to the APOE3/3 genotype were calculated under a logistic regression model.
For allelic association tests, OR, CI, and *P* associated with APOE2 allelic dose in APOE4 non-carriers (APOE2/2 < 2/3 < 3/3) and APOE4 allelic dose in APOE2 non-carriers (APOE4/4 > 3/4 > 3/3) in an additive genetic model were generated under a logistic regression model.

Reiman EM et al, *Nature Communication* 2020; Ward A *et al.,* Neuroepidemiology 2012

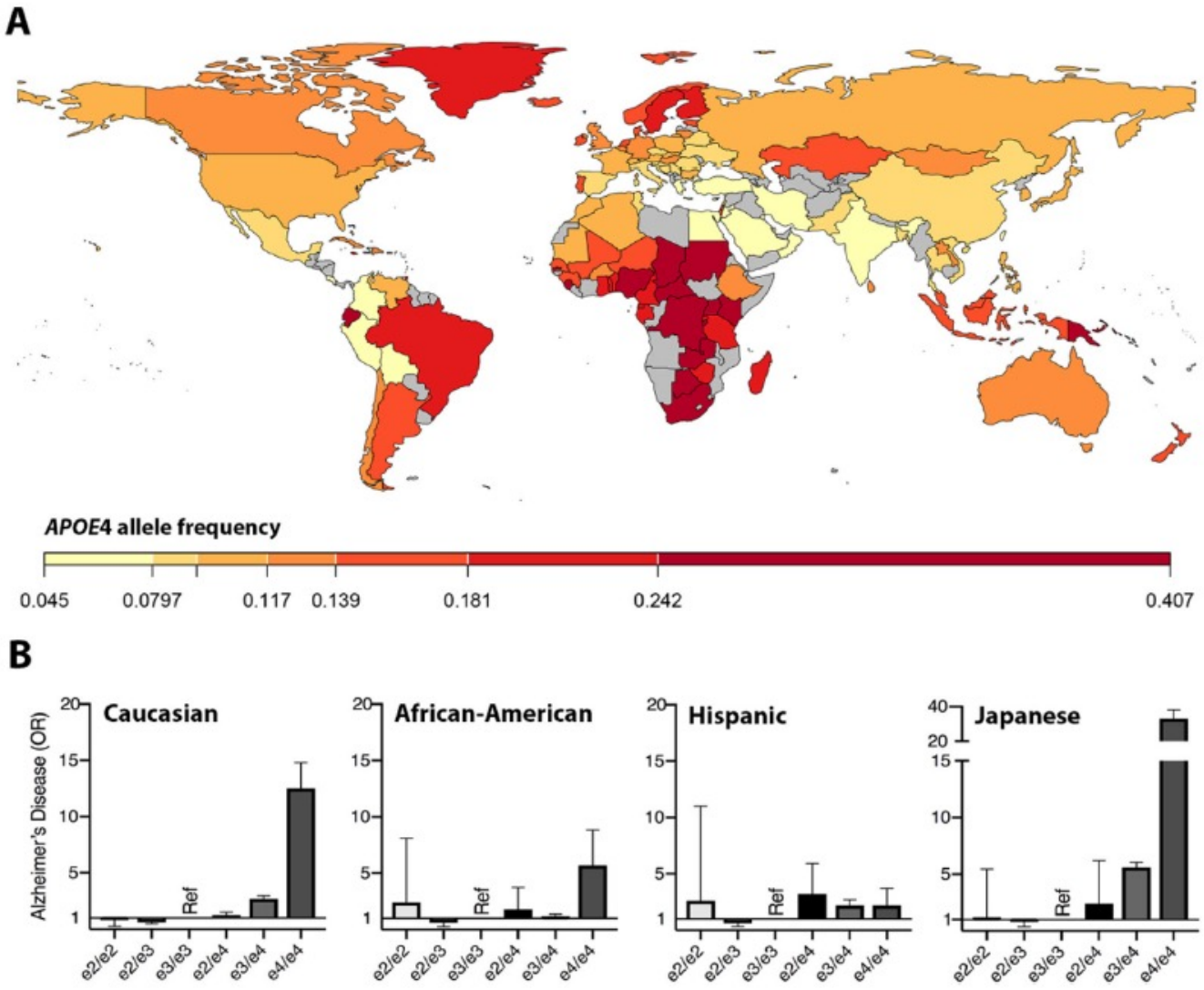
APOE genotype and Alzheimer's Disease (AD)

APOE4 carriers

- 20-25% general population
- 50-75% AD



The incidence and penetrance of APOE4 varies globally



APOE4 genotype and neurophysiological function

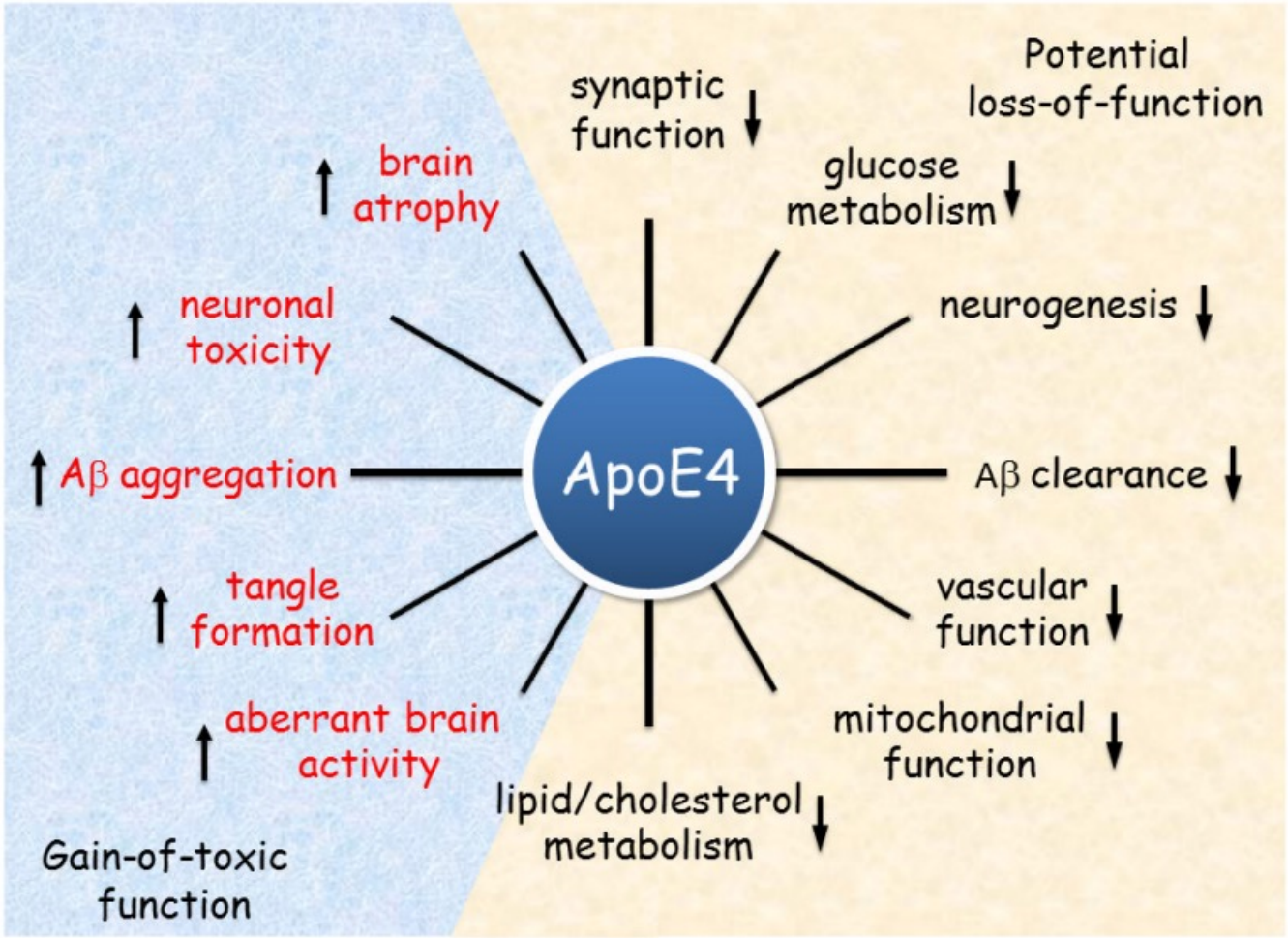


Figure 3. The role of Apolipoprotein E4 in Alzheimer disease pathogenesis

Neuroinflammation

Neurogenesis

Liu CC et al., Nat Rev Neurol. 2013

University of East Anglia | Norwich Medical School

APOE4 genotype and neurophysiological function

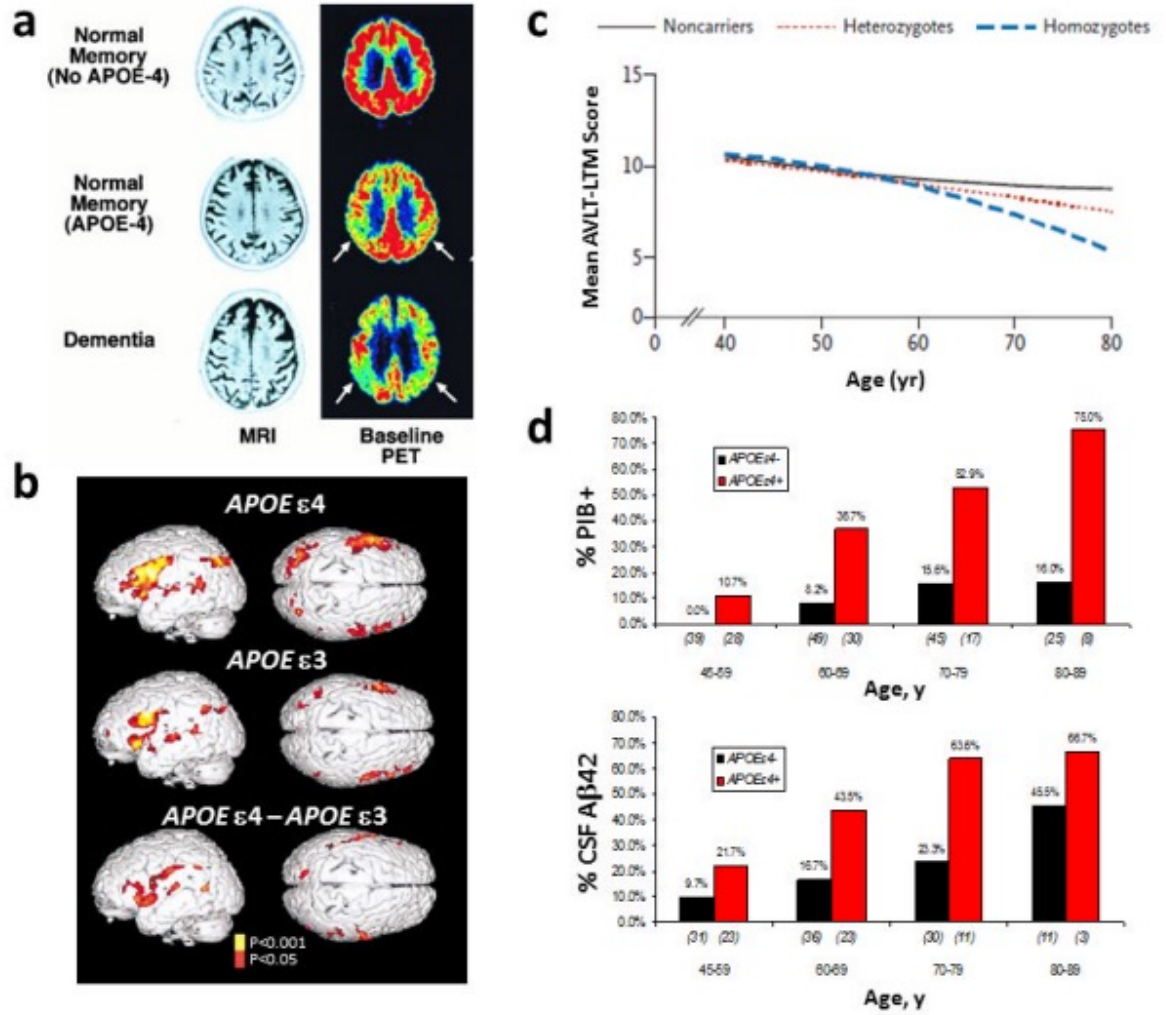
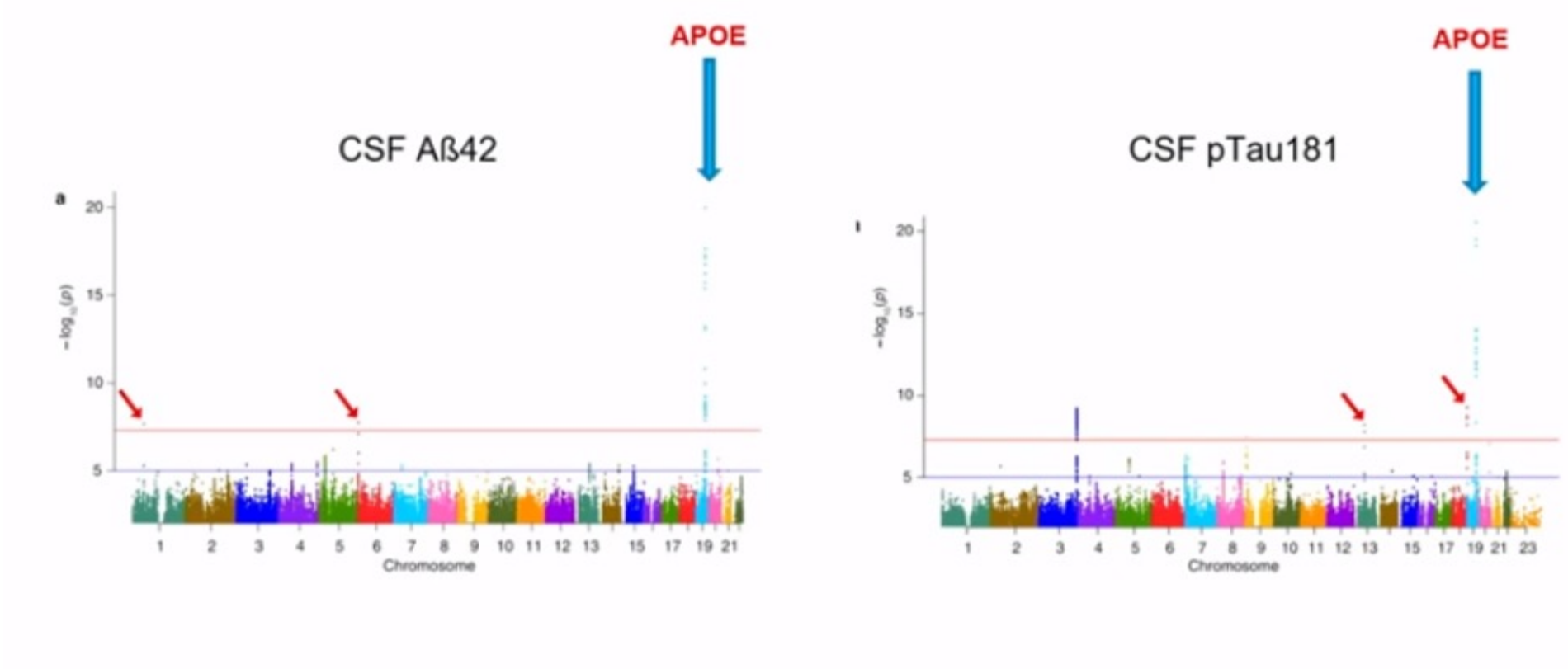


Figure 4. Abnormal brain function and enhanced neuropathology and memory decline in cognitively normal *APOE* ε4 carriers

(a) ^{18}F-fluorodeoxyglucose PET images show that cognitively normal *APOE* ε4 carriers have lower glucose metabolism than do noncarriers. (b) *APOE* ε4 carriers exhibit a greater increase in functional MRI signal in brain regions associated with task performance, and show increases in additional regions compared with *APOE* ε3 carriers. (c) Age-related memory decline occurs more rapidly in *APOE* ε4 carriers than noncarriers, starting from age 55–60 years. (d) *APOE* ε4 carriers show increased cerebral Aβ deposition which persists in greater frequencies with age compared with noncarriers. Increased PiB binding and reduced CSF $A\beta_{42}$ levels reflect cerebral amyloid deposition. Abbreviations: Aβ, amyloid-β; APOE,

Liu CC et al., Nat Rev Neurol. 2013

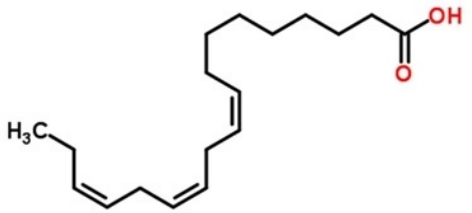
APOE4 genotype and neuropathology



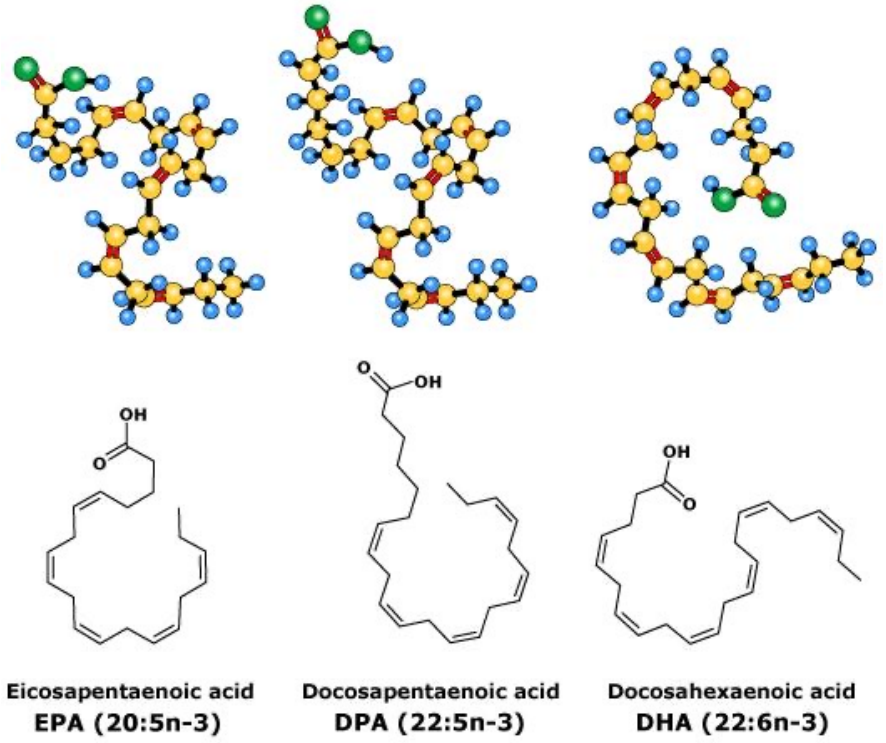
Deming Y et al., *Acta Neuropathol*. 2017

Poll 2

omega-3 fatty acids: the basics



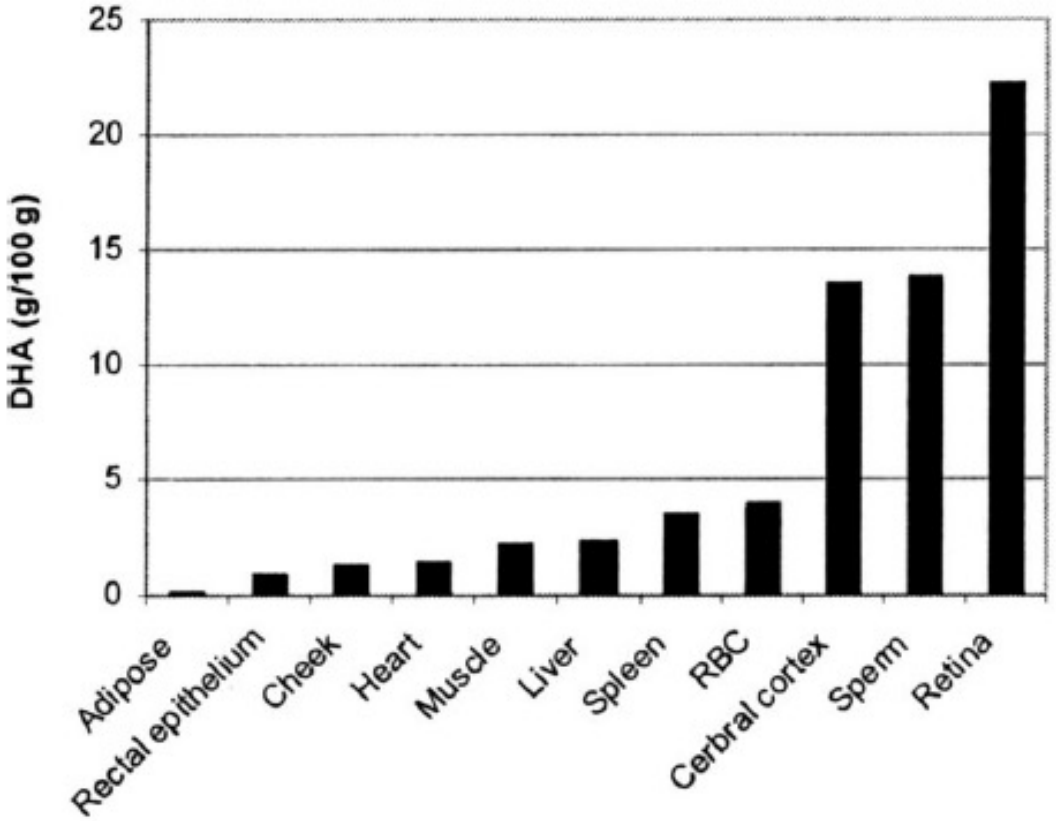
Alpha-linolenic acid (ALA)
$C_{18}H_{30}O_2$



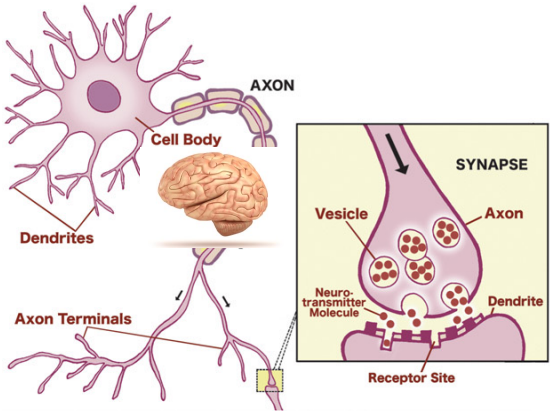
- ~500mg or 1g EPA/DHA per day for CVD primary and secondary prevention
- 2 portions of fish per week with one oily

SACN (Department of Health, UK), AHA (US)

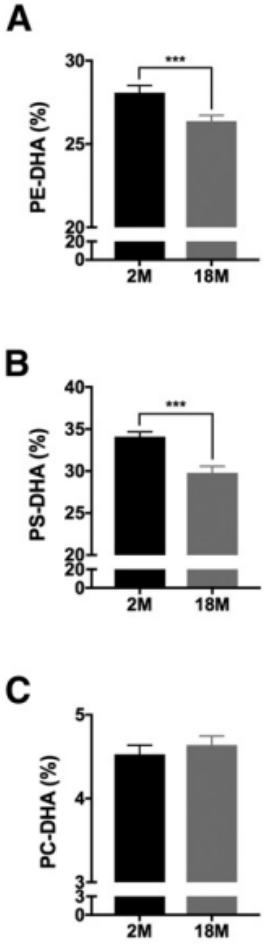
Brain tissue (and in particular synaptic region) is enriched in the n-3 fatty acid, DHA



Arterburn LM et al., *AJCN*, 2006



Synaptic membrane lipids up to 40% DHA



Martinsen A et al., *FASEB* 2019

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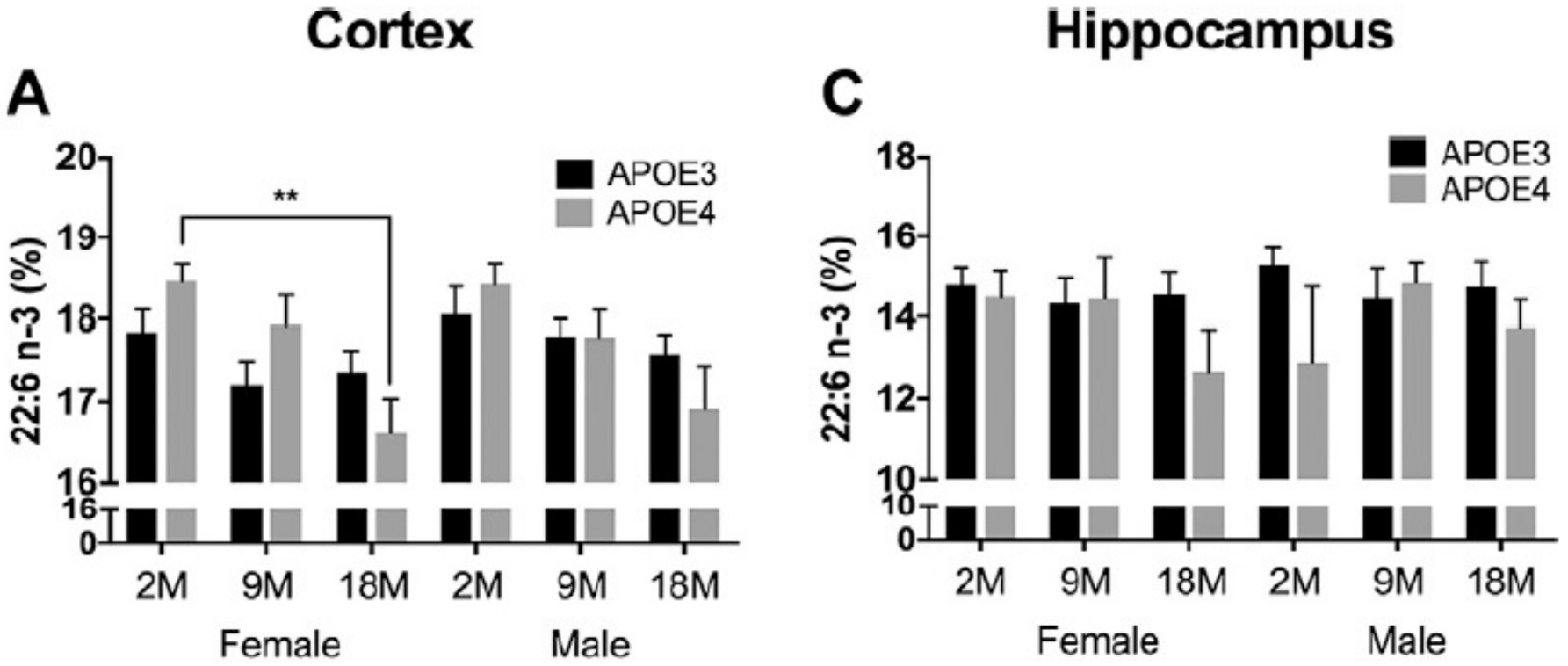
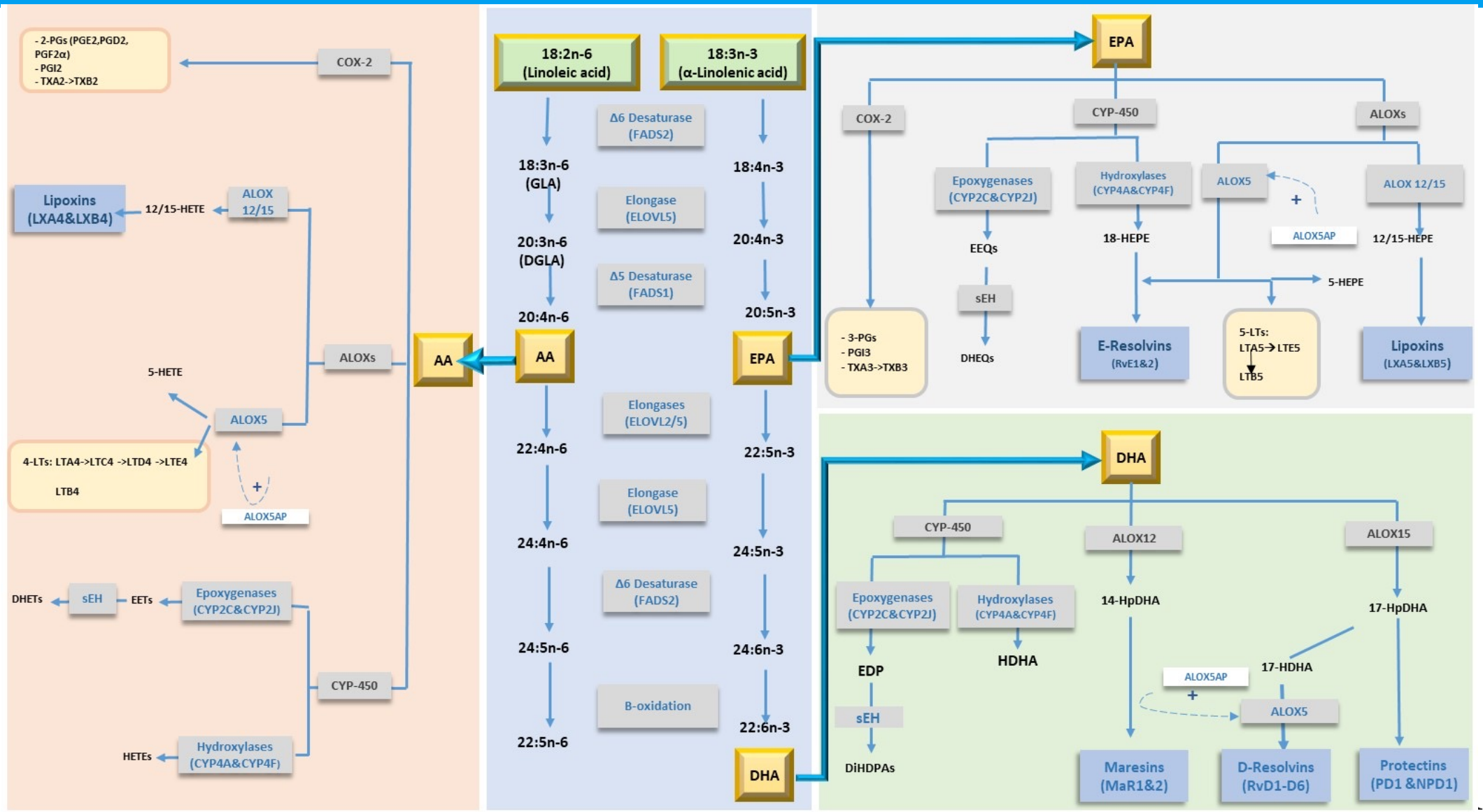
The effect of age, sex and *APOE4* on brain DHA levels



Martinsen A, Minihane et al. *FASEB* 2019

University of East Anglia | Norwich Medical School

Oxylipins and the resolution of inflammation



Schulze, Minihane, Saleh and Riserus, *Lancet Endocrin* 2020

Oxylipins mediate brain neuroinflammation

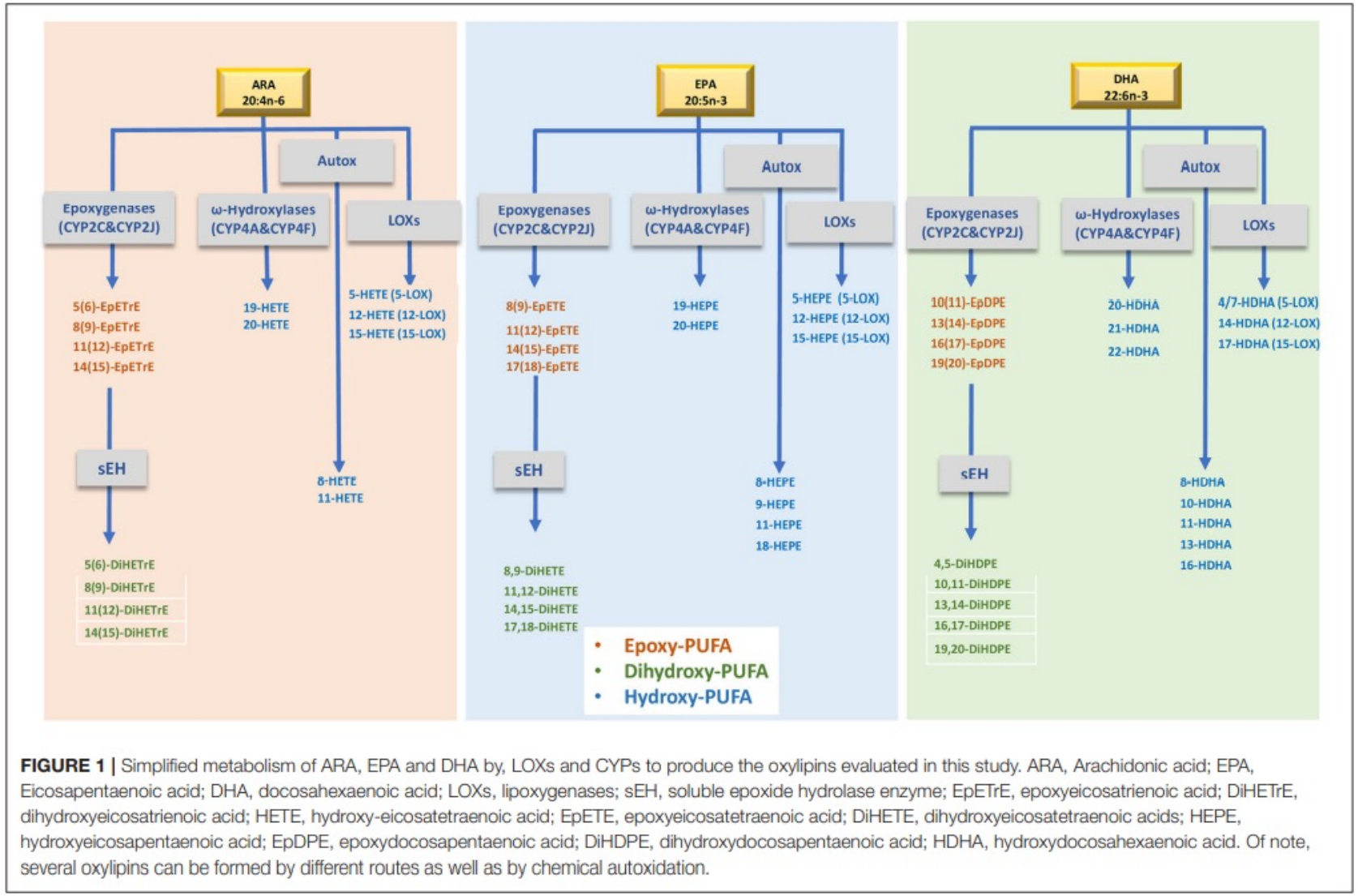


FIGURE 1 | Simplified metabolism of ARA, EPA and DHA by, LOXs and CYPs to produce the oxylipins evaluated in this study. ARA, Arachidonic acid; EPA, Eicosapentaenoic acid; DHA, docosahexaenoic acid; LOXs, lipoxygenases; sEH, soluble epoxide hydrolase enzyme; EpETrE, epoxyeicosatrienoic acid; DiHETrE, dihydroxyeicosatrienoic acid; HETE, hydroxy-eicosatetraenoic acid; EpETE, epoxyeicosatetraenoic acid; DiHETE, dihydroxyeicosatetraenoic acids; HEPE, hydroxyeicosapentaenoic acid; EpDPE, epoxydocosapentaenoic acid; DiHDPE, dihydroxydocosapentaenoic acid; HDHA, hydroxydocosahexaenoic acid. Of note, several oxylipins can be formed by different routes as well as by chemical autoxidation.

Schulze, Minihane, Saleh and Riserus, *Lancet Endocrin* 2020; Saleh R, Minihane AM *et al., Frontiers in Nutrition,* 2021

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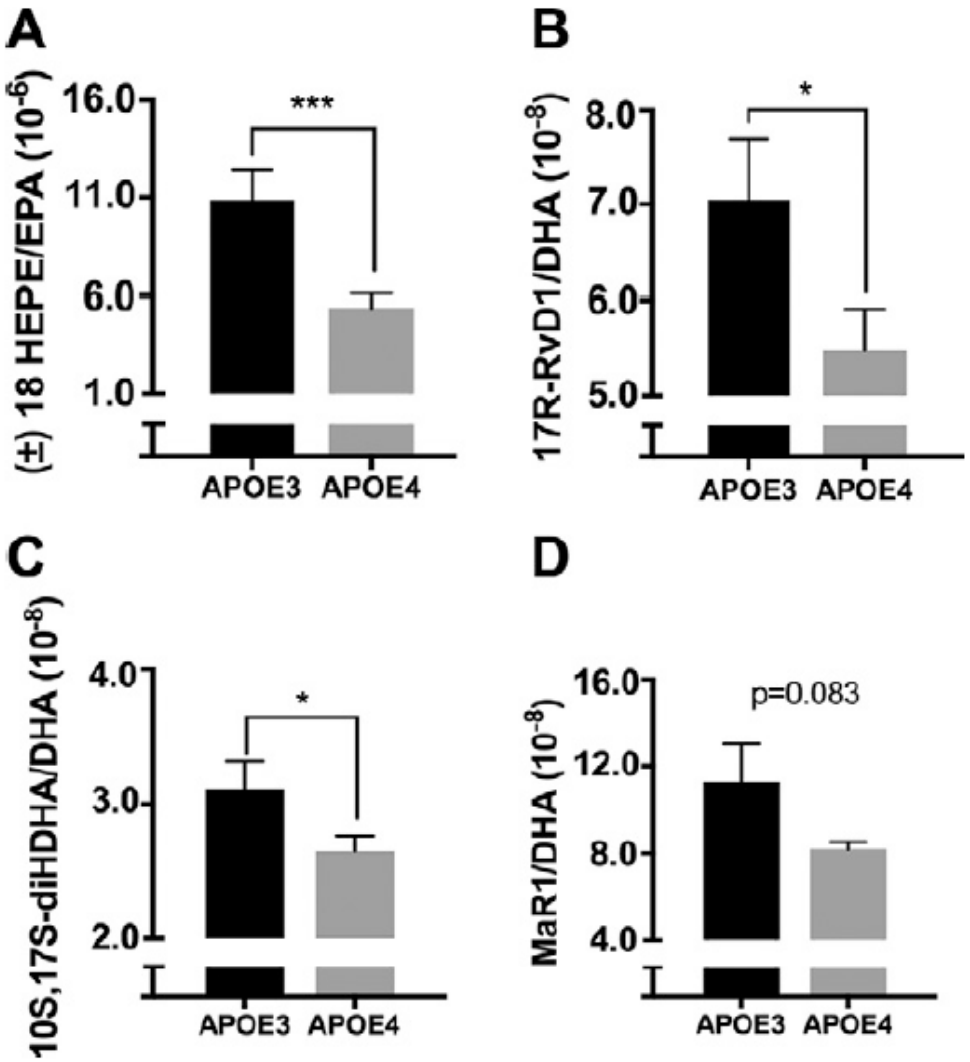
The effect *APOE4* on brain oxylipins



gure 5. Genotype differences in the ratios of SPMs to their
urent compound, EPA or DHA, in cortex of female and male
POE3 and *APOE4* mice at 2, 9, and 18 mo of age fed a chow
et. Figures of SPMs and their precursors were expressed in
g/mg of tissue to calculate the ratios. Values are means ±
M; $n = 20$/group. $^{*}P < 0.05$, $^{***}P < 0.001$.

Martinsen A, Minihane et al. *FASEB* 2019

APOE4 genotype and cognition penetrance affected by sex

APOE4 genotype and cognition penetrance affected by sex

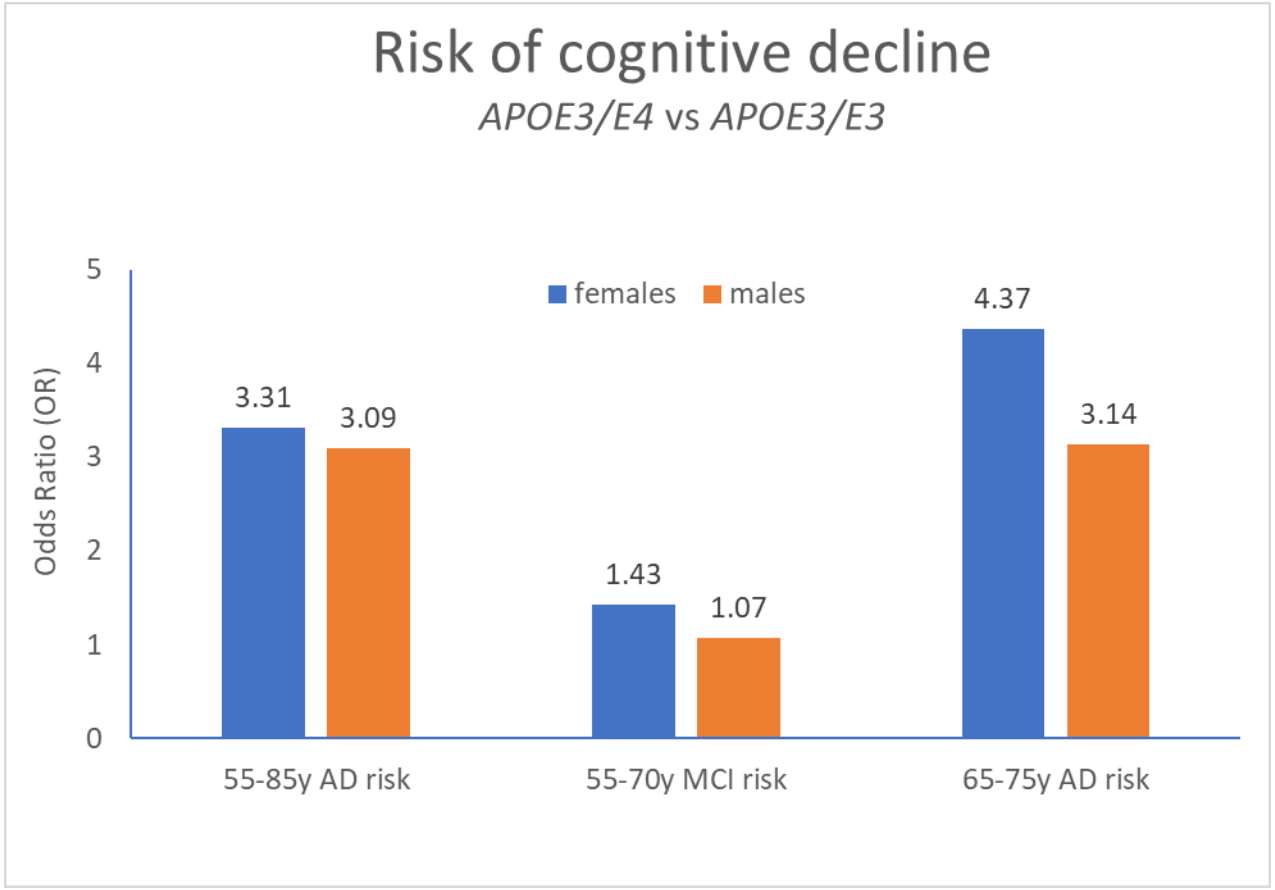
JAMA Neurology | Original Investigation

Apolipoprotein E Genotype and Sex Risk Factors for Alzheimer Disease

A Meta-analysis

Scott C. Neu, PhD; Judy Pa, PhD; Walter Kukull, PhD; Duane Beekly, BS; Amanda Kuzma, MS; Prabhakaran Gangadharan, MS; Li-San Wang, PhD; Klaus Romero, MD; Stephen P. Arneric, PhD; Alberto Redolfi, PhD; Daniele Orlandi, MsC; Giovanni B. Frisoni, MD; Rhoda Au, PhD; Sherral Devine, PhD; Sanford Auerbach, MD; Ana Espinosa, PhD; Mercè Boada, MD, PhD; Agustín Ruiz, MD, PhD; Sterling C. Johnson, PhD; Rebecca Koscik, PhD; Jiun-Jie Wang, PhD; Wen-Chuin Hsu, MD; Yao-Liang Chen, MD; Arthur W. Toga, PhD

JAMA Neurol. 2017;74(10):1178-1189.



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Summary so far

- Two thirds of those living with dementia are female
- *APOE4* females (12% population, 40-50% of AD) a high risk group with earlier onset, who may particularly benefit from intervention
- The affects of *APOE4* are pleiotropic with altered brain DHA concentrations and metabolism likely to be a contributing factor
- What interventions?

Lancet Commission Report: Modifiable risk factors for AD

The Lancet Commissions

Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission

Gill Livingston, Jonathan Huntley, Andrew Sommerlad, David Ames, Clive Ballard, Sube Banerjee, Carol Brayne, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Sergi G Costafreda, Amit Dias, Nick Fox, Laura N Gitlin, Robert Howard, Helen C Kales, Mika Kivimäki, Eric B Larson, Adesola Ogunniyi, Vasiliki Orgeta, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quincy Samus, Lon S Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam

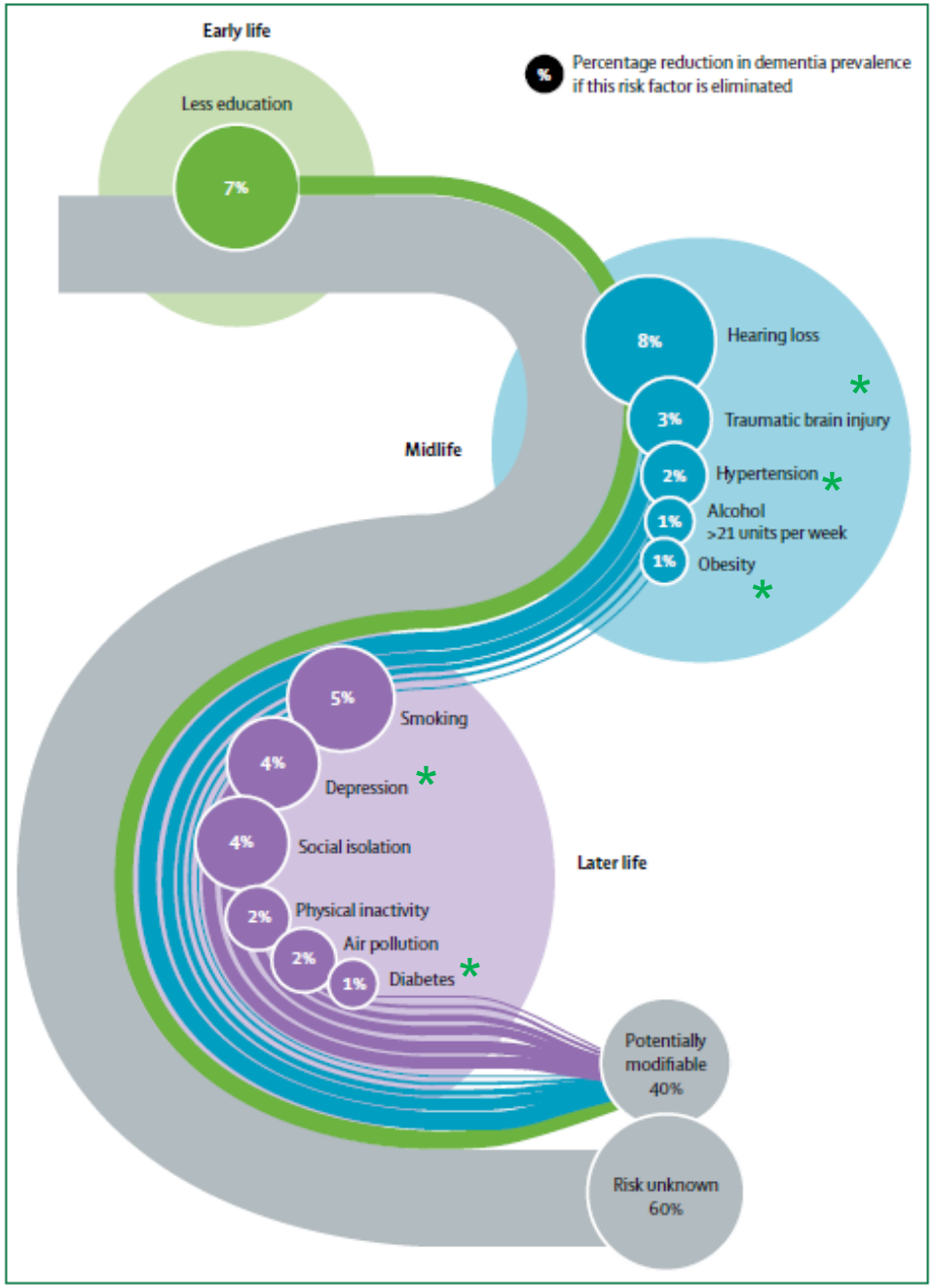

Figure 7: Population attributable fraction of potentially modifiable risk factors for dementia

Healthy lifestyle and the risk of Alzheimer dementia

Findings from 2 longitudinal studies

Klodian Dhana, MD, PhD, Denis A. Evans, MD, Kumar B. Rajan, PhD, David A. Bennett, MD, and Martha C. Morris, ScD

Neurology® 2020;95:e374-e383. doi:10.1212/WNL.0000000000009816

Correspondence
Dr. Dhana
klodian_dhana@rush.edu

Lifestyle score:

- Non-smoking,
- ≥150 min/week physical activity,
- light to moderate alcohol consumption,
- **high-quality diet**
- late-life cognitive activities

Score 4-5 vs 0-1 = HR 0.40, (95% CI 0.28–0.56) for AD

Increase score by 1 = HR 0.73, (95% CI 0.66–0.80) for AD

Lancet Commission 1: 2017

Lancet 2017; 390: 2673-734

The Lancet Commissions

Dementia prevention, intervention, and care

Gill Livingston, Andrew Sommerlad, Vasiliki Orgeta, Sergi G Costafreda, Jonathan Huntley, David Ames, Clive Ballard, Sube Banerjee, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Nick Fox, Laura N Gitlin, Robert Howard, Helen C Kales, Eric B Larson, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quincy Samus, Lon S Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam

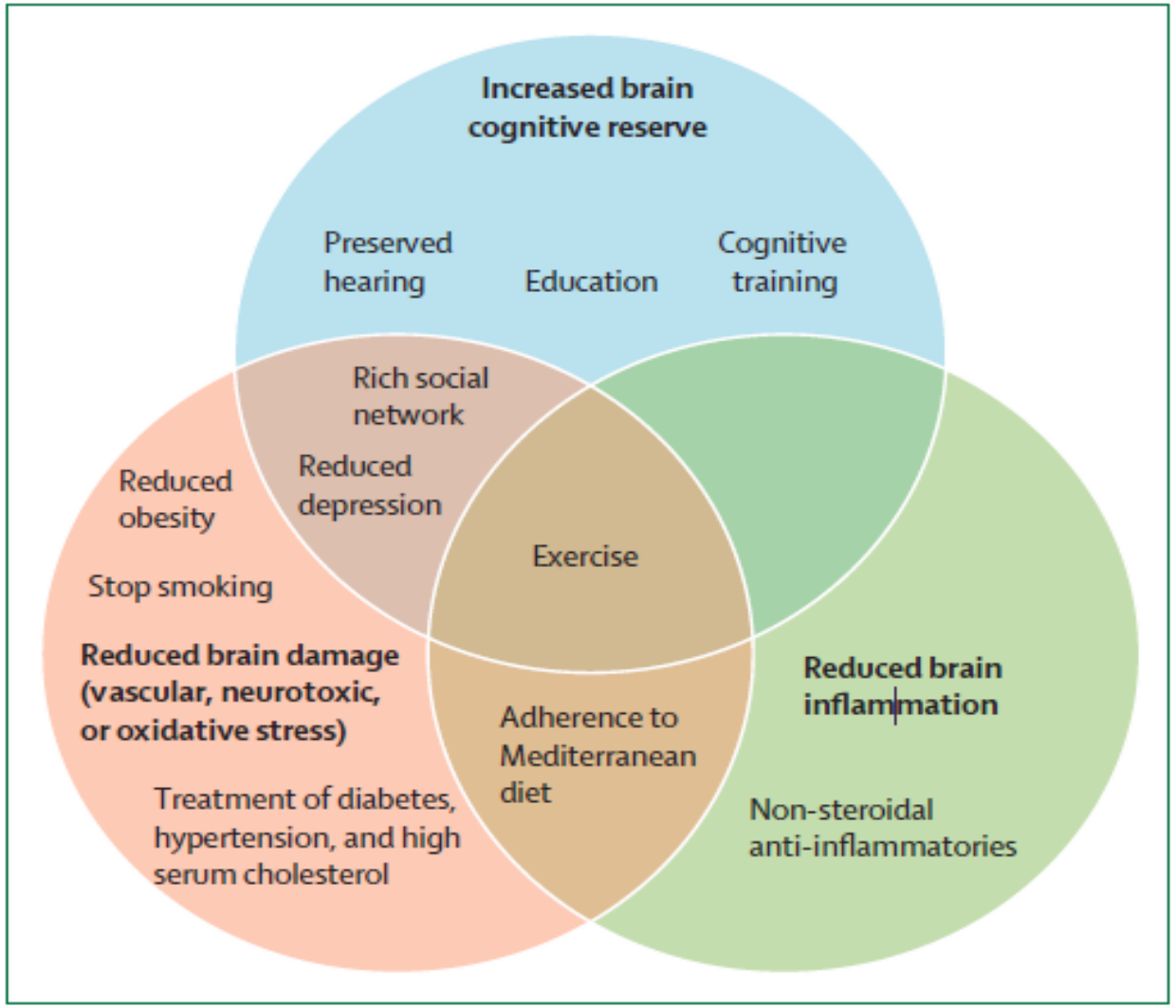

Figure 5: Potential brain mechanisms for preventive strategies in dementia

The Mediterranean Diet

FOOD GROUPS	GUIDANCE
Meats and sweets	Less often
Poultry, eggs, cheese and yogurt	Moderate portions, daily to weekly
Fish and seafood	Often, at least two times a week
Fruits, vegetables, grains (mostly whole), olive oil, beans, nuts, legumes, seeds, herbs and spices	Base every meal on these foods

Murphy and Minihane, *BJN* 2022

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14-point Mediterranean Diet Adherence Screener (MEDAS) Questionnaire

- Olive oil main cooking fat
- How much olive oil, □ 4 tablespoons per day
- Vegetables, □ 2 servings per day
- Fruit, □ 3 portions per day
- Meat, <1 portion per day
- Eat more poultry than red meat
- Fish/shellfish, □ 3 portions per week
- Butter, margarine, cream, <1 portion per day
- Legumes, □ 3 portions per week
- Nuts, □ 3 portions per week
- Tomato/onion/garlic/olive oil sauce, □ 2 portions per week
- Wine, >7 <14 units per week
- Sweet drinks, <1 per day
- Cakes/confectionaries, <3 portions per week

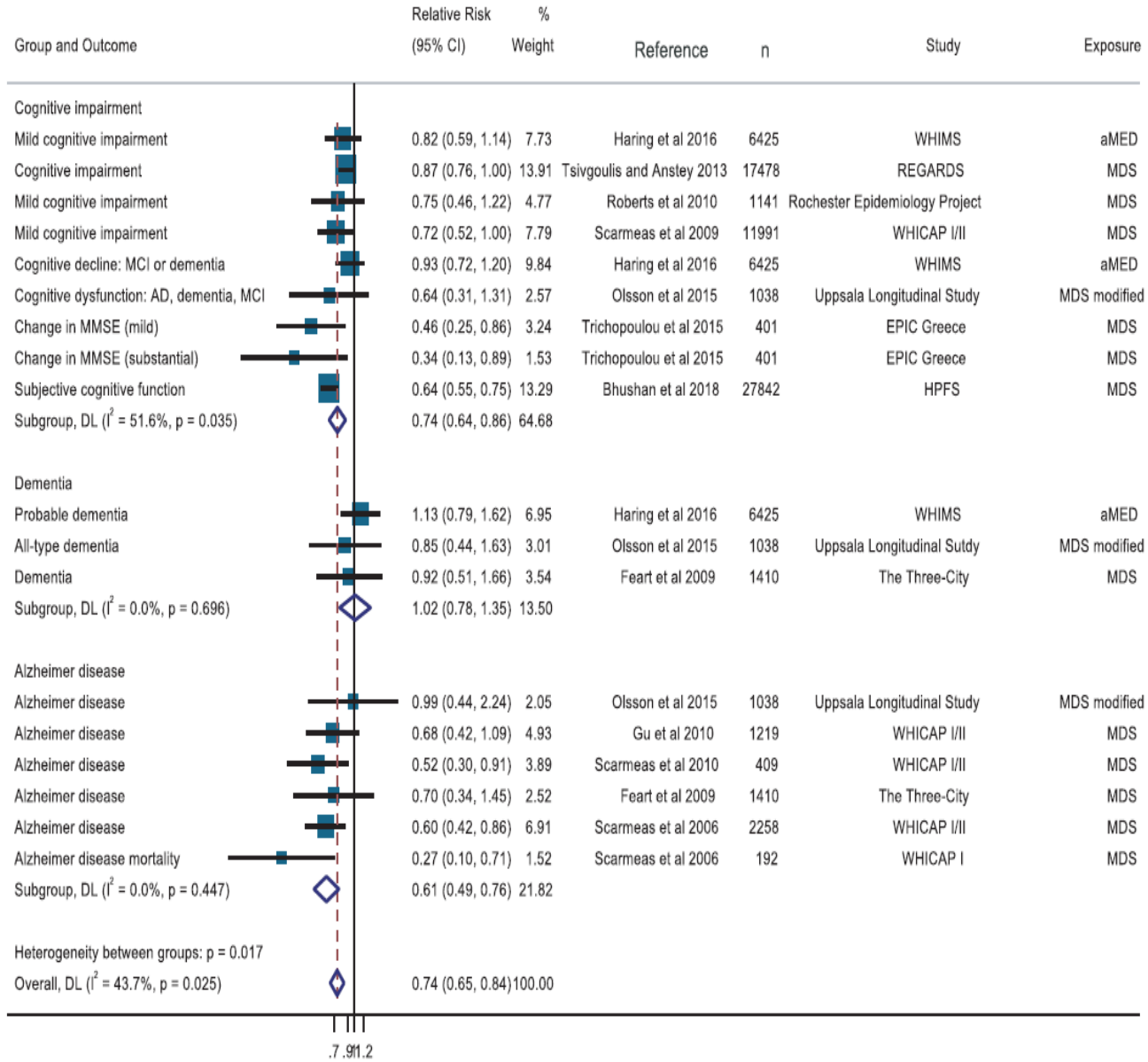
doi: 10.1111/joim.13333

The Mediterranean diet and health: a comprehensive overview

M. Guasch-Ferré[1,2] & W. C. Willett[1,2,3]

Guasch-Ferré M, Willett WC. The Mediterranean diet and health: a comprehensive overview. *J Intern Med* 2021; **290**: 549–566.

Mediterranean diet and cognitive function



Mediterranean dietary pattern (MDP) brain atrophy and neuropathology

MDP adherence, cross-sectional/longitudinal

- ↑ total brain, total gray matter, total white matter volume, mediotemporal and dentate gyrial volumes and cortical thickness (Luciano M et al, 2017; Staubo SC et al., 2017; Ballarini T et al., 2021; Gu Y et al., 2015; Karstens AJ et al., 2019; Zhang J et al., 2023)
- ↓ PiB-PET deposition in AD-affected regions (Berti V et al., Neurology 2018; Vassilaki M et al., 2018)
- ↑ FDG-PET glucose metabolism and higher (Berti V et al., Neurology 2018)
- CSF ↑ β-amyloid42/40, ↓ pTau181, and modulated the association between CSF β-amyloid42/40/ pTau181 and atrophy (Ballarini T et al., 2021)

RESEARCH ARTICLE Open Access

Mediterranean diet adherence is associated with lower dementia risk, independent of genetic predisposition: findings from the UK Biobank prospective cohort study

Oliver M. Shannon[1†], Janice M. Ranson[2†], Sarah Gregory[3], Helen Macpherson[4], Catherine Milte[4], Marleen Lentjes[5], Angela Mulligan[6], Claire McEvoy[7], Alex Griffiths[8], Jamie Matu[8], Tom R. Hill[1], Ashley Adamson[1], Mario Siervo[9], Anne Marie Minihane[10,11], Graciela Muniz-Tererra[3,12], Craig Ritchie[3], John C. Mathers[1*], David J. Llewellyn[2,13†] and Emma Stevenson[1†]

Shannon *et al. BMC Medicine* (2023) 21:81
https://doi.org/10.1186/s12916-023-02772-3

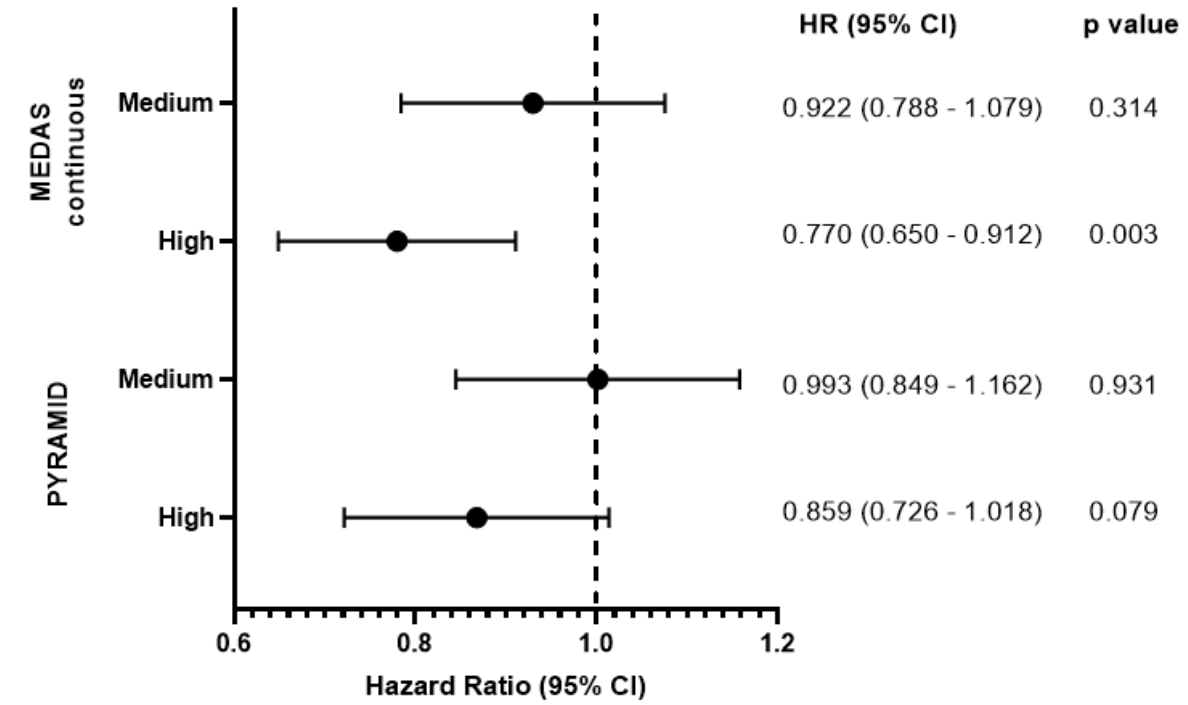
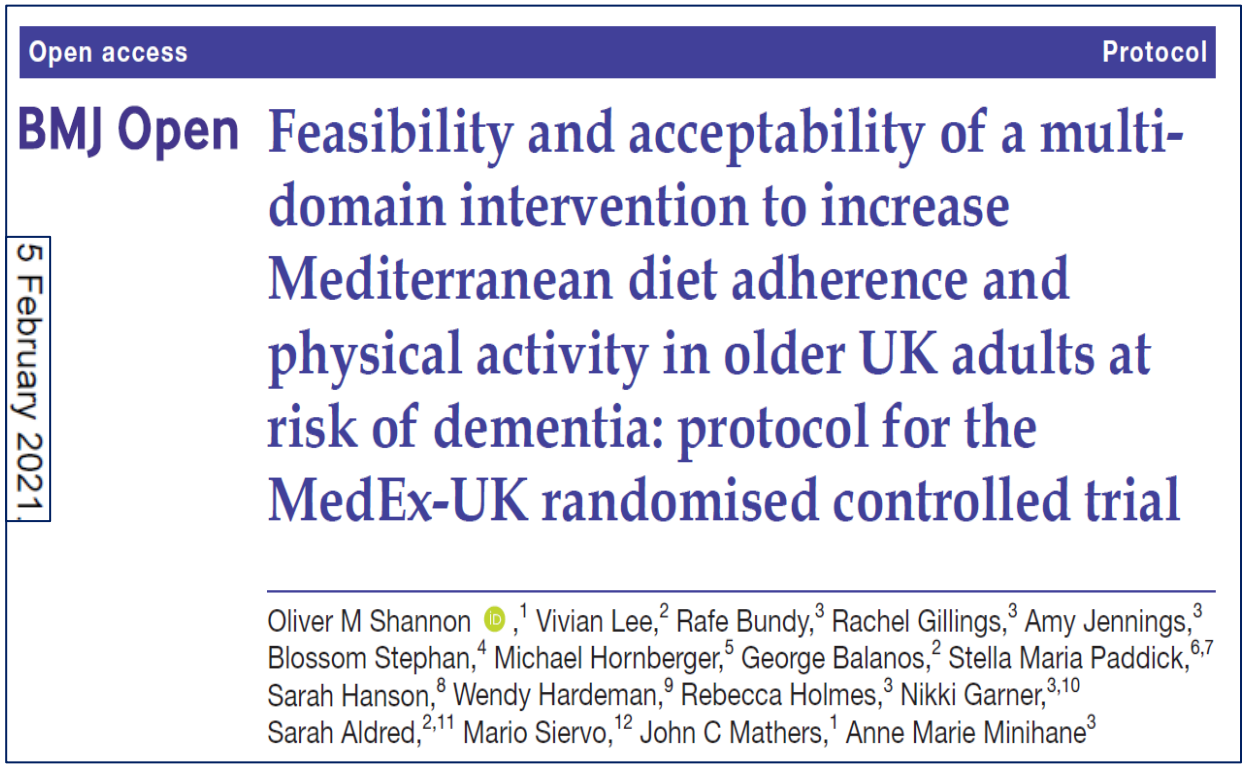


Fig. 1. Association between MedDiet adherence and risk of dementia (n = 60298, including 882 dementia cases). MedDiet adherence level was split into tertiles, with the dashed line reflecting the low MedDiet adherence reference group for each MedDiet score.

- No polygenic risk score or *APOE* genotype * MDP interaction
- No education attainment * MDP interaction

- No one dietary component drove the impact of the MDP

MedEx (2018-2021), AppleTree (2019-2024)



Open access Protocol

BMJ Open 5 February 2021

Feasibility and acceptability of a multi-domain intervention to increase Mediterranean diet adherence and physical activity in older UK adults at risk of dementia: protocol for the MedEx-UK randomised controlled trial

Oliver M Shannon ,[1] Vivian Lee,[2] Rafe Bundy,[3] Rachel Gillings,[3] Amy Jennings,[3] Blossom Stephan,[4] Michael Hornberger,[5] George Balanos,[2] Stella Maria Paddick,[6,7] Sarah Hanson,[8] Wendy Hardeman,[9] Rebecca Holmes,[3] Nikki Garner,[3,10] Sarah Aldred,[2,11] Mario Siervo,[12] John C Mathers,[1] Anne Marie Minihane[3]

Alzheimer's Research UK

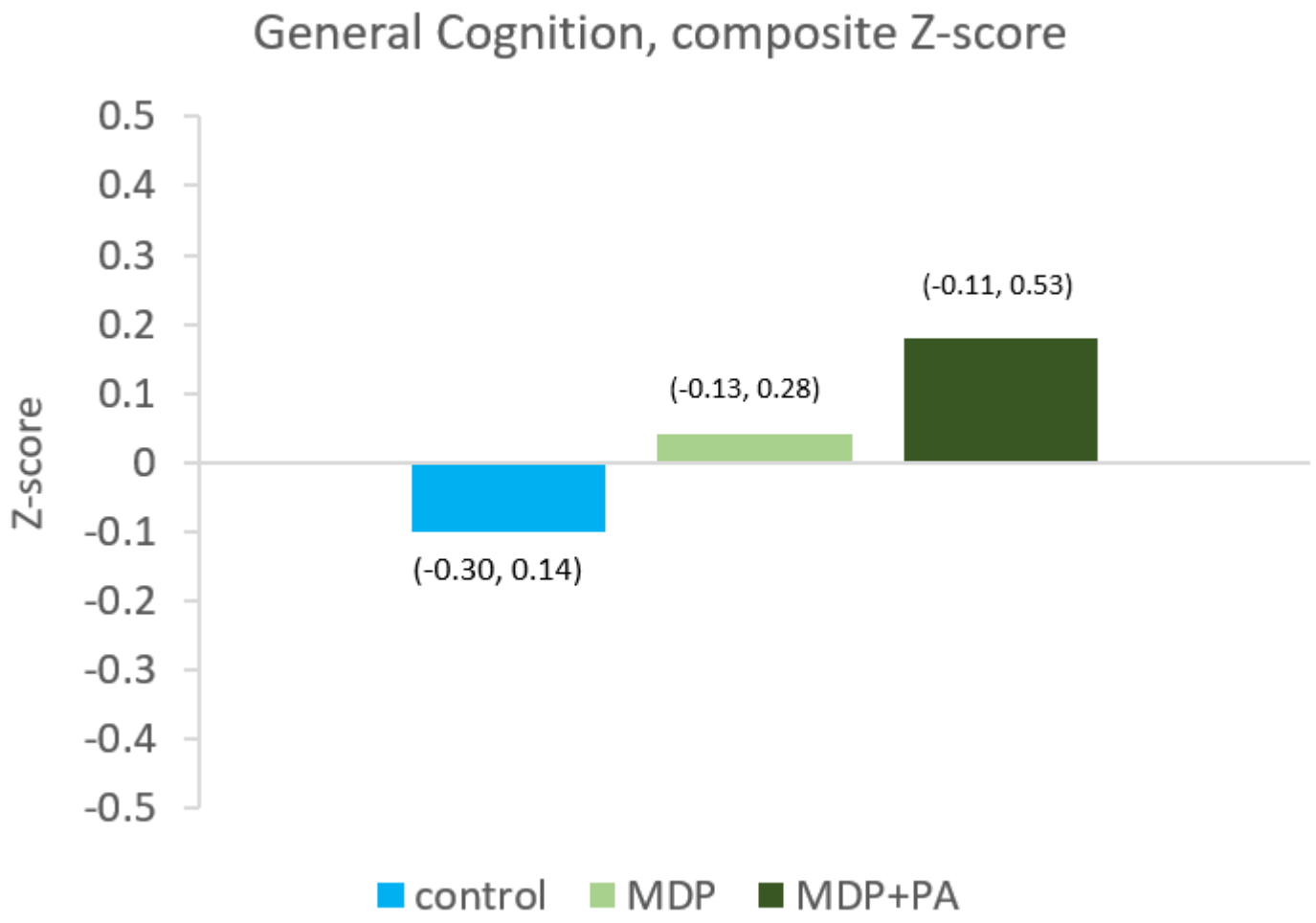
UK Nutrition Research Partnership (UK NRP) Collaborative Awards
(NuBrain, 2019-2023)

MRC Medical Research Council

NHS National Institute for Health Research

UKRI Economic and Social Research Council

RESULTS: Neurocognitive Test Battery



P1 <0.01
P2 <0.01
P3 =0.06

P1 = p-value for ANCOVA (dependent variable= value at 24 weeks; independent variables= treatment group, baseline value, study site and baseline BMI).

P2 = p-value for contrast 1: Control v. (MD + MDPA)

P3 = p-value for contrast 2: MD v. MDPA

2021

Cochrane Library

Cochrane Database of Systematic Reviews

Multi-domain interventions for the prevention of dementia and cognitive decline (Review)

Hafdi M, Hoevenaar-Blom MP, Richard E

Participants at increased risk of dementia and cognitive decline: *Effect by ApoE4 genotype* .
Two studies (FINGER 2015; MAPT 2017) reported their results stratified by ApoE4 genotype (carrier or noncarrier) accounting for a total of 585 carriers of ApoE4 and 1458 noncarriers of ApoE4. There was high-certainty evidence that cognitive functioning measured by a NTB Z-score slightly improved in ApoE4 carriers receiving a multi-domain intervention (MD 0.14, 95% CI 0.04 to 0.25) but not in noncarriers (MD 0.04, 95% CI -0.02 to 0.10, P for interaction 0.09).

JAMA Neurology | Original Investigation

Effect of the Apolipoprotein E Genotype on Cognitive Change During a Multidomain Lifestyle Intervention

A Subgroup Analysis of a Randomized Clinical Trial

Alina Solomon, MD, PhD; Heidi Turunen, BM; Tiia Ngandu, MD, PhD; Markku Peltonen, PhD; Esko Levälahti, MSc; Seppo Helisalmi, PhD; Riitta Antikainen, MD, PhD; Lars Bäckman, PhD; Tuomo Hänninen, PhD; Antti Jula, MD, PhD; Tiina Laatikainen, MD, PhD; Jenni Lehtisalo, MSc; Jaana Lindström, PhD; Teemu Paajanen, MA, Psy; Satu Pajala, PhD; Anna Stigsdotter-Neely, PhD; Timo Strandberg, MD, PhD; Jaakko Tuomilehto, MD, PhD; Hilkka Soininen, MD, PhD; Miia Kivipelto, MD, PhD

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)

American Journal of Epidemiology

DOI: 10.1093/aje/kwx330

Original Contribution

Fish Intake, Genetic Predisposition to Alzheimer Disease, and Decline in Global Cognition and Memory in 5 Cohorts of Older Persons

Cécilia Samieri*, Martha-Clare Morris, David A. Bennett, Claudine Berr, Philippe Amouyel, Jean-François Dartigues, Christophe Tzourio, Daniel I. Chasman, and Francine Grodstein

* Correspondence to Dr. Cécilia Samieri, Bordeaux Population Health Research Center, INSERM, U1219, and University of Bordeaux, ISPED, CS 61292, 146 rue Léo-Saignat, 33076 Bordeaux, France (e-mail: cecilia.samieri@u-bordeaux.fr).

Initially submitted May 31, 2017; accepted for publication October 3, 2017.

Fish are a primary source of long-chain omega-3 fatty acids, which may help delay cognitive aging. We pooled participants from the French Three-City study and 4 US cohorts (Nurses' Health Study, Women's Health Study, Chicago Health and Aging Project, and Rush Memory and Aging Project) for whom diet and cognitive data were available (n = 23,688 white persons, aged ≥65 years, 88% female, baseline year range of 1992–1999, and median follow-up range of 3.9–9.1 years) to investigate the relationship of fish intake to cognitive decline and examine interactions with genes related to Alzheimer disease. We estimated cohort-specific associations between fish and change in composite scores of global cognition and episodic memory using linear mixed models, and we pooled results using inverse-variance weighted meta-analysis. In multivariate analyses, higher fish intake was associated with slower decline in both global cognition and memory (P for trend ≤ 0.031). Consuming ≥4 servings/week versus <1 serving/week of fish was associated with a lower rate of memory decline: 0.018 (95% confidence interval: 0.004, 0.032) standard units, an effect estimate equivalent to that found for 4 years of age. For global cognition, no comparisons of higher versus low fish intake reached statistical significance. In this meta-analysis, higher fish intake was associated with a lower rate of memory decline. We found no evidence of effect modification by genes associated with Alzheimer disease.

Alzheimer dementia; cognitive aging; gene-environment interaction; omega-3 fatty acids

Prospective cohort study evidence is highly supportive of cognitive benefits of n-3 fatty acids, particularly DHA

0.1-0.2g DHA per day is associated with:

- ✓ Improved performance on a range of cognitive tests including memory and executive function
- ✓ 30-40% reduced risk of Alzheimer's Disease risk and deaths
- ✓ Higher total and hippocampal brain volume

Evidence of greater benefits in females

Hosseini M et al., 2020; Pontifex, Vauzour and Minihane, 2018; Conquer JA et al., 2000; Schaefer E et al., 2006, Lopez LB et al., 2011; Tan ZS et al., 2012. Yassine H et al., 2016; Fraser T et al., 2010; Zhang Y et al., 2016, Zhang Y et al., 2016 and 2018; Coughlan G et al., 2021

APOE4 affects brain EPA and DHA uptake following intervention

Yassine *et al. Alzheimer's Research & Therapy* (2016) 8:25
DOI 10.1186/s13195-016-0194-x

Alzheimer's Research & Therapy

RESEARCH Open Access

The effect of APOE genotype on the delivery of DHA to cerebrospinal fluid in Alzheimer's disease

Hussein N. Yassine[1*], Varun Rawat[1], Wendy J. Mack[2], Joseph F. Quinn[3], Karin Yurko-Mauro[4], Eileen Bailey-Hall[4], Paul S. Aisen[5], Helena C. Chui[6] and Lon S. Schneider[6,7]

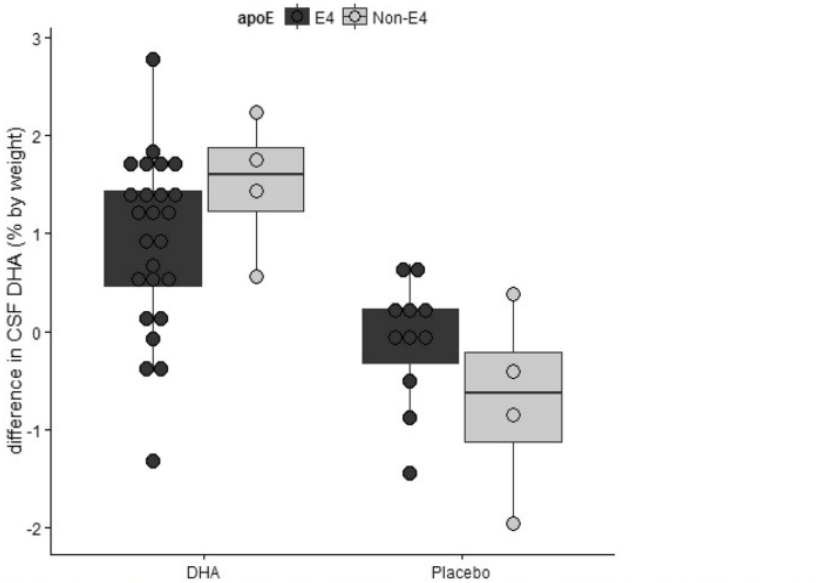
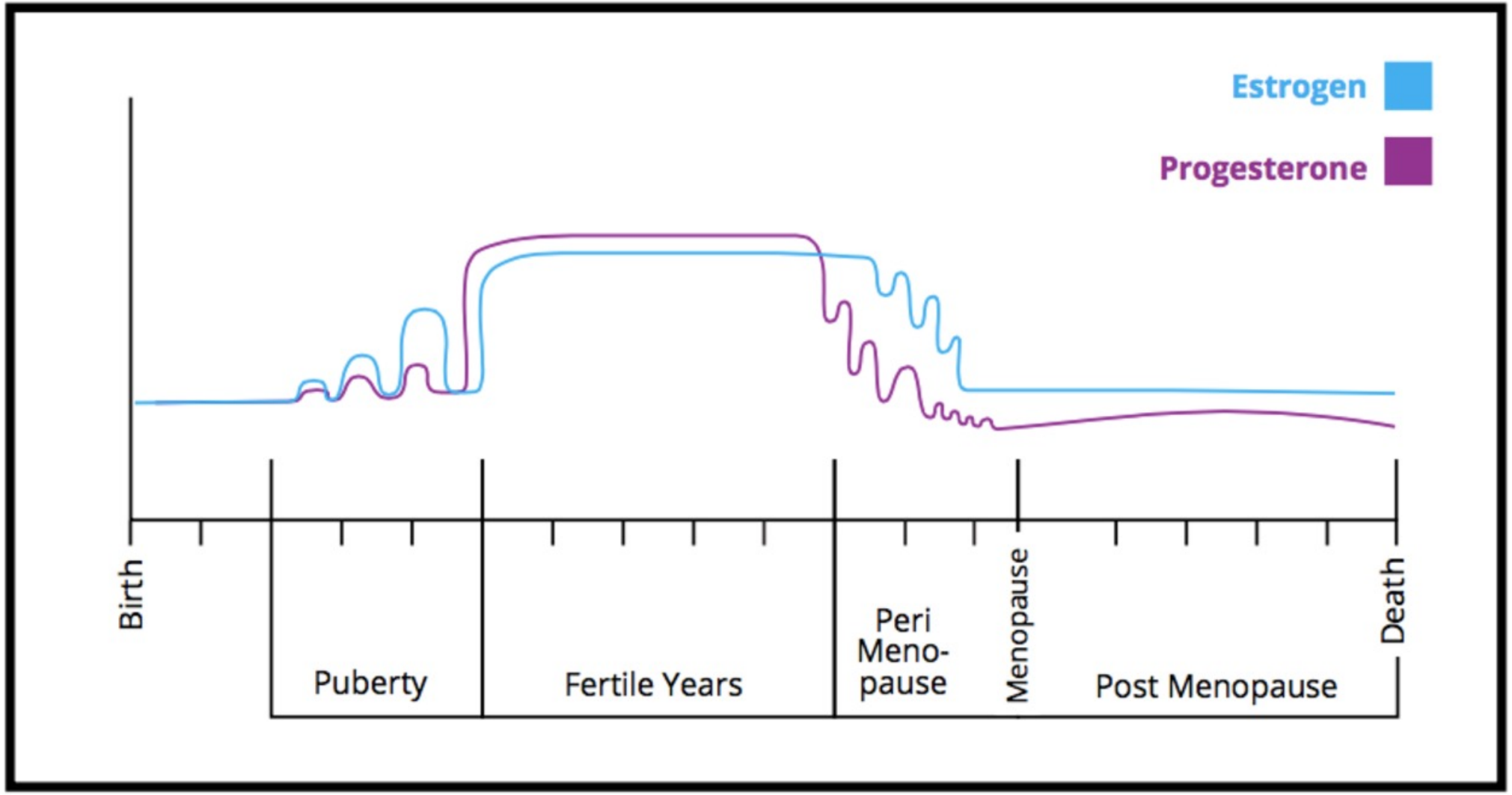


Fig. 5 Change in CSF DHA by *APOE* status and treatment arm. The effect of DHA treatment vs. placebo on CSF DHA levels by *APOE* genotype is illustrated. The increases in DHA levels in the CSF were less pronounced in carriers of the ε4 allele. All ε4 noncarriers had increased CSF DHA levels after allocation to DHA treatment. In contrast, 6 of the 25 ε4 carriers did not increase DHA levels after DHA supplementation. There was a suggestion for an interaction effect between *APOE* genotype and treatment arm on CSF DHA levels ($p = 0.07$). The data were modeled using multivariate linear regression with the change in CSF DHA as the dependent variable and *APOE* and treatment arm as the independent variables. *Aβ42* amyloid-β42, *APOE* apolipoprotein E, *CSF* cerebrospinal fluid, *DHA* docosahexaenoic acid

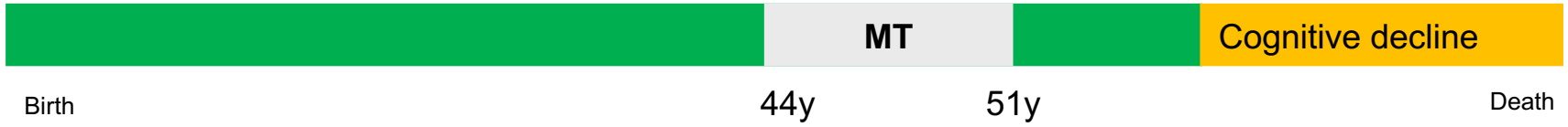
Summary so far

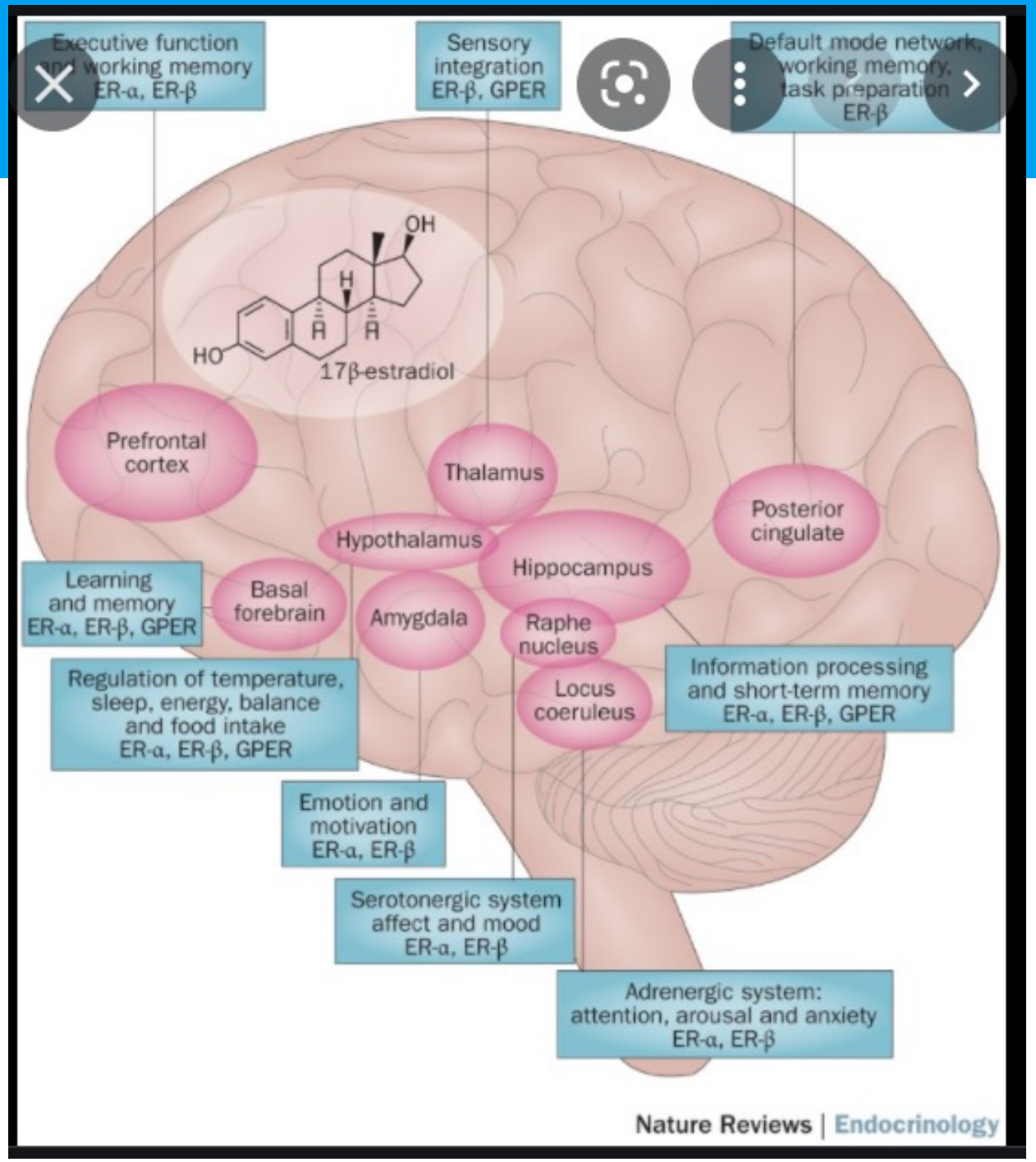
- Mediterranean diet and MIND diets associated with improved cognition, lower AD risk, and effective in *APOE4*
- *APOE4* lower DHA (omega-3) status
- In *APOE4* higher dose of DHA and earlier long term intervention are recommended

Hormone changes throughout life



Menopause and the menopausal transition (MT)





Brinton D et al., 2016

Menopause, *brain fog,* long term cognition and HRT

- Concentration
- Memory
- Verbal fluency

- Sleep
- Mood/depression
- Anxiety

Menopause and cognition

OPEN

Menopause impacts human brain structure, connectivity, energy metabolism, and amyloid-beta deposition

Lisa Mosconi[1,2,3]✉, Valentina Berti[4], Jonathan Dyke[2], Eva Schelbaum[1], Steven Jett[1], Lacey Loughlin[1], Grace Jang[1], Aneela Rahman[1], Hollie Hristov[1], Silky Pahlajani[1,2], Randolph Andrews[5], Dawn Matthews[5], Orli Etingin[6], Christine Ganzer[7], Mony de Leon[2], Richard Isaacson[1] & Roberta Diaz Brinton[8]

Scientific Reports | (2021) 11:10867

What is the effect of menopause on cognition, brain fatty acids profiles and synaptic function according to *APOE* genotype

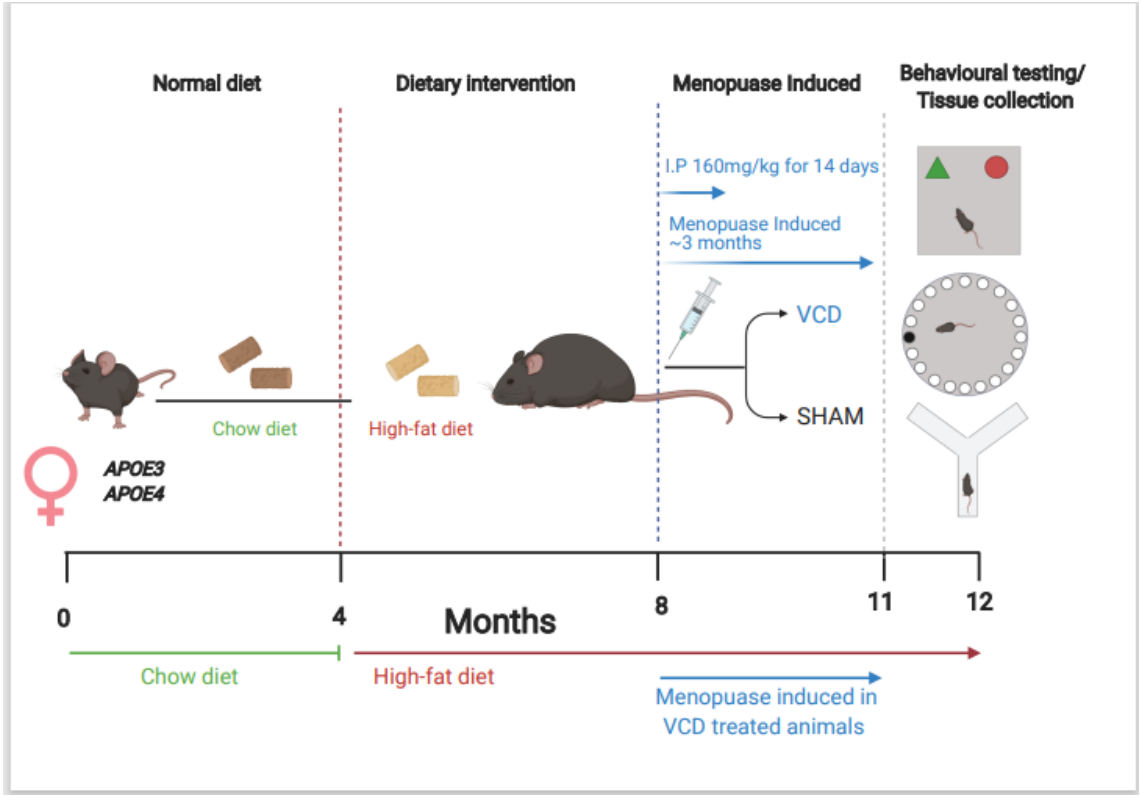
Received: 1 December 2020 | Revised: 19 March 2021 | Accepted: 25 March 2021
DOI: 10.1096/fj.202002621RR

RESEARCH ARTICLE

THE FASEB JOURNAL

APOE4 genotype exacerbates the impact of menopause on cognition and synaptic plasticity in APOE-TR mice

Matthew G. Pontifex | Anneloes Martinsen | Rasha Noureldin M. Saleh | Glenn Harden | Noemi Tejera | Michael Müller | Chris Fox | David Vauzour | Anne-Marie Minihane



nutrients

Article

DHA-Enriched Fish Oil Ameliorates Deficits in Cognition Associated with Menopause and the *APOE4* Genotype in Rodents

Matthew G. Pontifex [1,*], Anneloes Martinsen [1], Rasha N. M. Saleh [1,2], Glenn Harden [1], Chris Fox [1,3], Michael Muller [1], David Vauzour [1,†] and Anne-Marie Minihane [1,†]

Pontifex M, Minihane et al. *FASEB* 2021, *Nutrients* 2022

University of East Anglia | Norwich Medical School

Poll 3

What is in HRT?

- Oestrogen
- Progesterone
- Testosterone

- Oral
- Transdermal (Skin patch, Gel, Spray)
- Vaginal

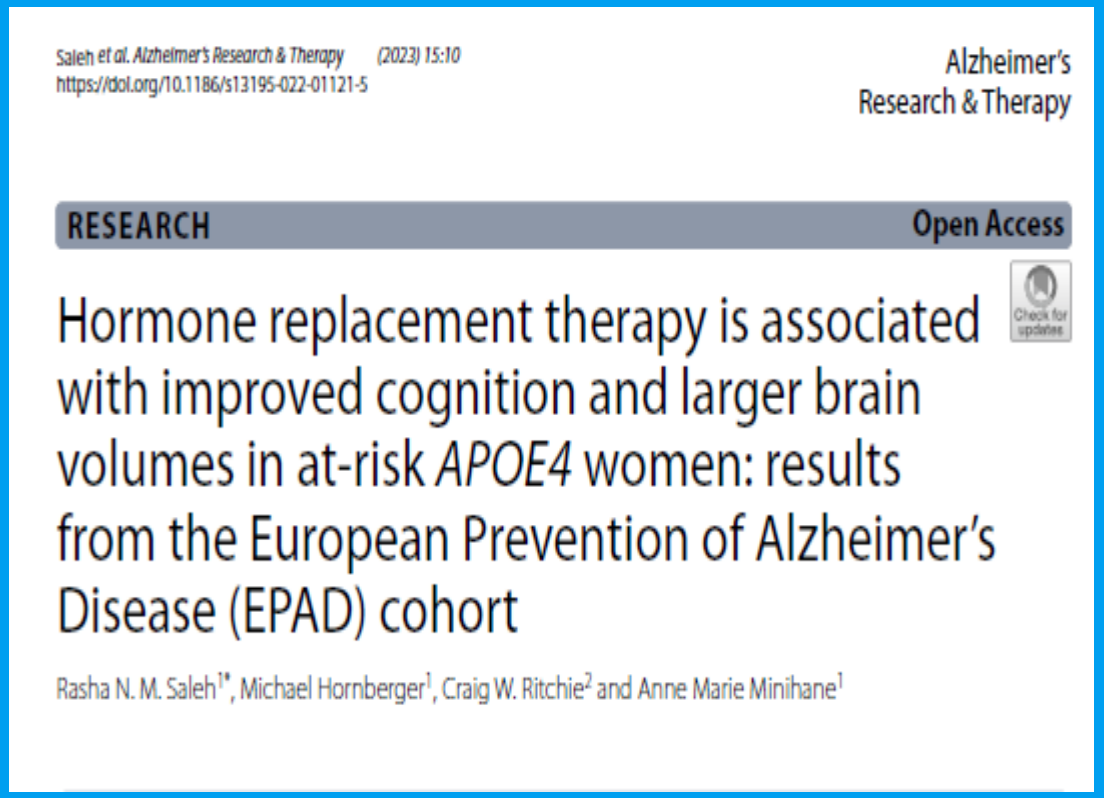
- Natural/body identical
- Synthetic

HRT and cognition, dementia

- Early observation studies -> HRT could be protective against dementia (Yaffe K et al., *JAMA* 1998; Mills , Faull and Kwakowsky, *Int J Med* 2023)

- Clinical trials results -> inconsistent/null/harmful (WHIMS, Schumaker S et al., *JAMA* 2004: KEEPS, Gleason CE et al., *PloS Medicine* 2015; ELITE, Henderson VW et al., *Neurology* 2016)

- Effect of age of HRT use?
- Effect of *APOE* genotype?



Saleh et al. Alzheimer's Research & Therapy (2023) 15:10
https://doi.org/10.1186/s13195-022-01121-5

Alzheimer's
Research & Therapy

RESEARCH Open Access

Hormone replacement therapy is associated with improved cognition and larger brain volumes in at-risk *APOE4* women: results from the European Prevention of Alzheimer's Disease (EPAD) cohort

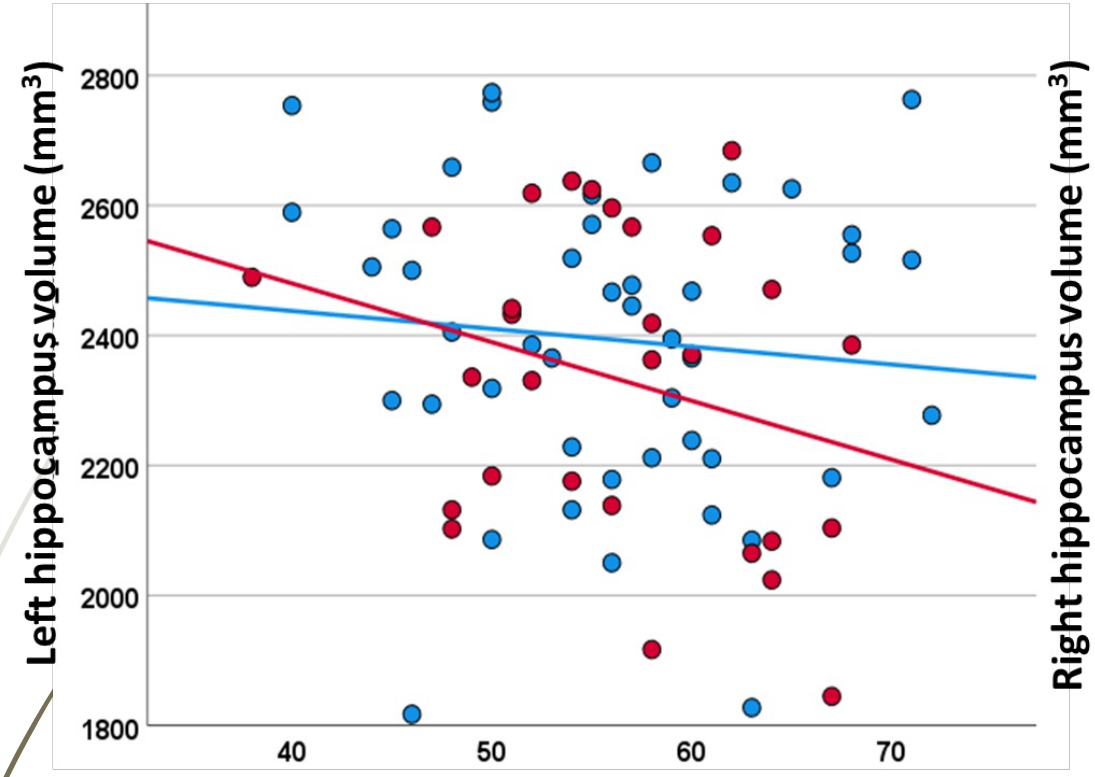
Rasha N. M. Saleh[1*], Michael Hornberger[1], Craig W. Ritchie[2] and Anne Marie Minihane[1]

- total n= 1906, women= 1178, 55.9%
- Cognition
- Brain MRI

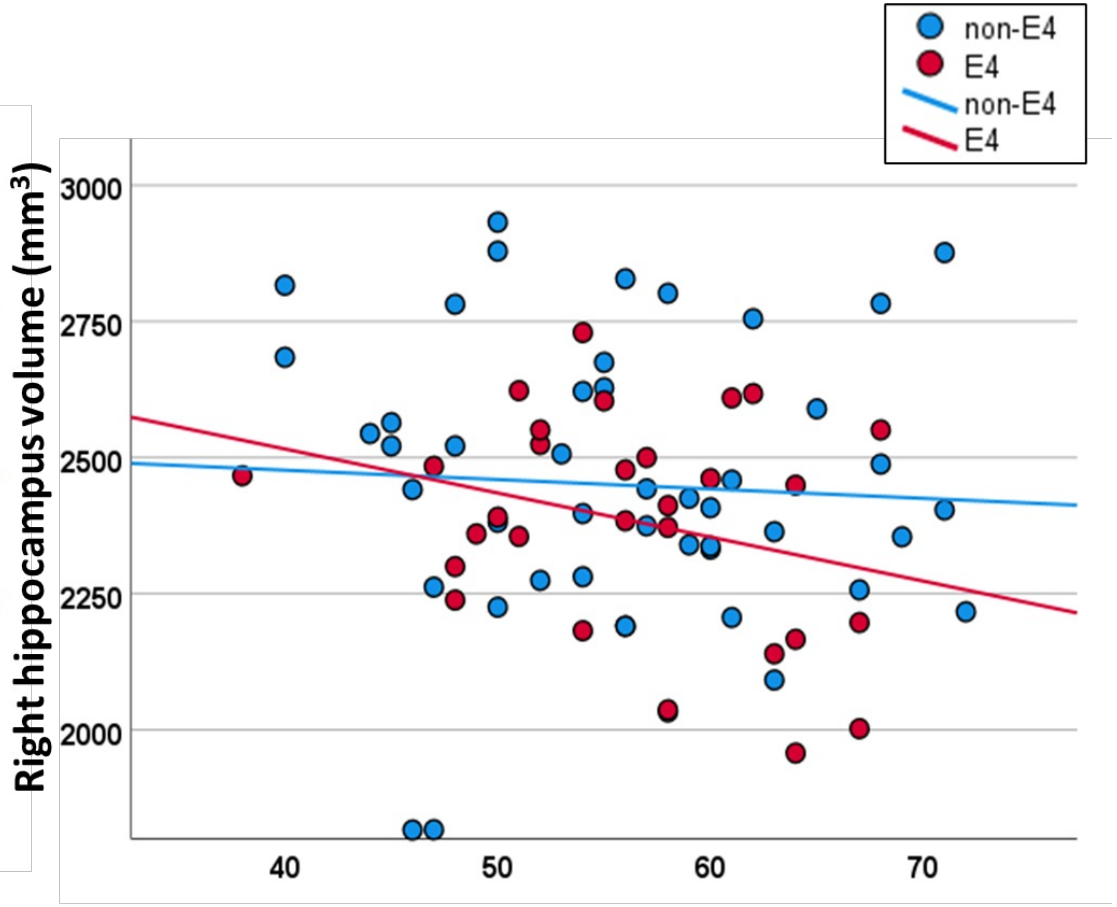
Key findings

- HRT is associated with improved RBANS delayed memory index in *APOE4* only
- HRT use is associated with larger (6-10%) medial temporal lobe (MTL volumes) in *APOE4* only
- Earlier HRT intervention is associated with larger hippocampal volume in *APOE4* only

University of East Anglia | Norwich Medical School



Non-*APOE4*: standardized β= 0.268 (p=0.349)
APOE4: standardized β= -0.577 (p=0.028)

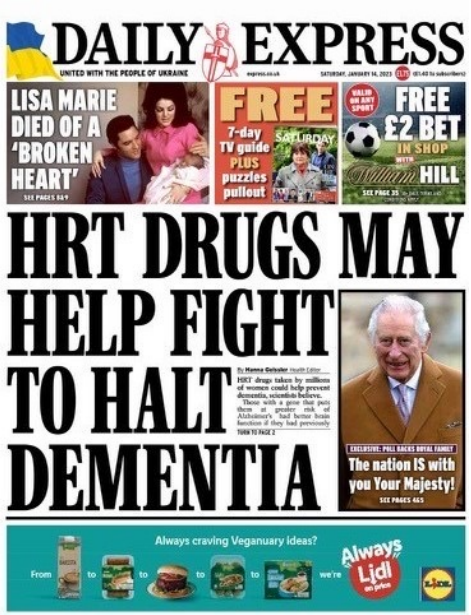


Non-*APOE4*: standardized β= 0.310 (p=0.271)
APOE4: standardized β= -0.555 (p=0.035)

Saleh et al. *Alzheimer's Research & Therapy, 2023*

HRT, *APOE*, cognition and brain volume

The Guardian reports University of East Anglia (UEA) researchers say although they can not say for sure that HRT cut dementia risk in women, the findings were "really important" amid limited drug options for dementia and an urgent



T3

Journal of Alzheimer's Disease 53 (2016) 547–556
DOI 10.3233/JAD-160258
IOS Press

Early Postmenopausal Transdermal 17β-Estradiol Therapy and Amyloid-β Deposition

Kejal Kantarci[a,*], Val J. Lowe[a], Timothy G. Lesnick[b], Nirubol Tosakulwong[b], Kent R. Bailey[b], Julie A.Fields[c], Lynne T. Shuster[d], Samantha M. Zuk[a], Matthew L. Senjem[e], Michelle M. Mielke[b,f], Carey Gleason[g], Clifford R. Jack, Jr.[a], Walter A. Rocca[b,f] and Virginia M. Miller[h]

Conclusion: In this pilot study, transdermal 17β-estradiol therapy in recently postmenopausal women was associated with a reduced amyloid-β deposition, particularly in *APOE* ε4 carriers. This finding may have important implications for the prevention of AD in postmenopausal women, and needs to be confirmed in a larger sample.

Summary final part

- Perimenopause is associated with neurocognitive disturbances. Longer term impact on neurocognitive decline?

- Perimenopause window of intervention opportunity in women to reduce life-long risk of dementia

- Indication *APOE4* more susceptible to menopause?

- Early HRT may have some cognitive benefits in *APOE4.* Confirmation in RCT needed

UEA, Norwich, UK
Anneloes Martinsen, Matthew Pontifex, Rasha Saleh, David Vauzour

Glasgow University, UK
Muriel Caslake, Chris Packard et al.

University of Reading, UK
Virtu Calabuig-Navarro, Esti Olano-Martin, Andrew Carvalho-Wells, Christine Williams, Kim Jackson, Julie Lovegrove,

Newcastle University, UK
- John Mather, Peter Curtis (now UEA) et al.

University of Southampton, UK
Philip Calder, Elizabeth Miles et al.,

CANN Collaborators
UEA: David Vauzour, Aedín Cassidy (now QUB), Rachel Gillings, Michael Irvine,
North Carolina, US: Colin Kay
KCL, London: Kim Min, Cristina Legido-Quigley
Melbourne, Australia: Andrew Scholey, David White, Rebecca King
University of Illinois, US: Hilary Schwarb, Neal J Cohen,

Food Standards Agency
wellcome trust
BBSRC bioscience for the future
Abbott A Promise for Life
Alzheimer's Society United Against Dementia
UEA University of East Anglia | Norwich Medical School
Athena SWAN Silver Award

a.minihane@uea.ac.uk

@ProfAMMinihane

University of East Anglia | Norwich Medical School

Athena SWAN Silver Award

When is HRT not recommended_NICE 2022

- Breast cancer
- Other oestrogen-dependent cancer
- Thromboembolism
- Untreated endometrial hyperplasia
- Angina, heart attack, stroke
- Blood clotting disorder
- Liver disease

<u>Prescribe with caution</u>

- Diabetes mellitus (increased risk of heart disease)
- Risk of venous thromboembolism
- History of endometrial hyperplasia
- Migraine and migraine-like headaches
- Increased risk of breast cancer

Additional Questions

Use this contact information
if you have additional questions
from today's webinar

Anne Marie Minihane, Phd,
Professor Of Nutrigenetics
Email: a.minihane@uea.ac.uk

Thank you for listening!

- a.minihane@uea.ac.uk