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
• 944,000 cases UK
• 16.5% of mortality women
• 8.7% of mortality men
• 1/14 over 65y
• 1/6 over 80y
Poll 1
65% of people living with dementia are women.


35% of people living with dementia are men.

Dementia.....

- Higher age-standardised prevalence in women

(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

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<tr>
<td>1%</td>
<td>12%</td>
<td>2%</td>
<td>63%</td>
<td>20%</td>
<td>2%</td>
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**APOE genotype and longevity**

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

- **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.

<table>
<thead>
<tr>
<th>APOE</th>
<th>Neuropathologically confirmed group</th>
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<th>Neuropathologically unconfirmed group</th>
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<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>P</td>
<td>OR</td>
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<tr>
<td>Genotype</td>
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<tr>
<td>2/2</td>
<td>0.13</td>
<td>0.05-0.36</td>
<td>6.3 × 10⁻⁵</td>
<td>0.52</td>
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<td>2/3</td>
<td>0.39</td>
<td>0.30-0.50</td>
<td>1.6 × 10⁻¹²</td>
<td>0.63</td>
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<tr>
<td>2/4</td>
<td>2.68</td>
<td>1.65-4.36</td>
<td>7.5 × 10⁻⁵</td>
<td>2.47</td>
</tr>
<tr>
<td>3/4</td>
<td>6.13</td>
<td>5.08-7.41</td>
<td>2.2 × 10⁻⁷</td>
<td>3.55</td>
</tr>
<tr>
<td>4/4</td>
<td>31.22</td>
<td>16.59-58.75</td>
<td>4.9 × 10⁻²⁵</td>
<td>10.70</td>
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<tr>
<td>Allelic dose</td>
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<tr>
<td>2</td>
<td>0.38</td>
<td>0.30-0.48</td>
<td>1.1 × 10⁻¹⁵</td>
<td>0.64</td>
</tr>
<tr>
<td>4</td>
<td>6.00</td>
<td>5.06-7.12</td>
<td>3.4 × 10⁻⁹⁰</td>
<td>3.43</td>
</tr>
</tbody>
</table>

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.
**APOE genotype and Alzheimer’s Disease (AD)**

### APOE4 carriers
- 20-25% general population
- 50-75% AD

**APOE genotype, odds ratio (OR, 95% CI) and average age of onset of Alzheimer’s Disease (AD)**

- **E3/E3**, OR 1.0, 84y
- **E3/E4**, OR 4.3, 76y
- **E4/E4**, OR 15.6, 68y

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13/06/2023
The incidence and penetrance of APOE4 varies globally
APOE4 genotype and neurophysiological function

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

Liu CC et al., Nat Rev Neurol. 2013
APOE4 genotype and neurophysiological function

Figure 4. Abnormal brain function and enhanced neuropathology and memory decline in cognitively normal APOE e4 carriers
(a) 18F-fluorodeoxyglucose PET images show that cognitively normal APOE e4 carriers have lower glucose metabolism than do noncarriers. (b) APOE e4 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 e3 carriers. (c) Age-related memory decline occurs more rapidly in APOE e4 carriers than noncarriers, starting from age 55–60 years. (d) APOE e4 carriers show increased cerebral Aβ deposition which persists in greater frequencies with age compared with noncarriers. Increased PiB binding and reduced CSF Aβ42 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
omega-3 fatty acids: the basics

- ~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.

Martinsen A et al., FASEB 2019

Synaptic membrane lipids up to 40% DHA

Arterburn LM et al., AJCN, 2006
The effect of age, sex and APOE4 on brain DHA levels

Martinsen A, Minihane et al. FASEB 2019
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, lipoxigenases; sEH, soluble epoxide hydrolase; EpETE, epoxyeicosatrienoic acid; DHETE, dihydroxyeicosatrienoic acid; HETE, hydroxy-eicosatetraenoic acid; EpETE, epoxyeicosatrienoic acid; DHETE, dihydroxyeicosatetraenoic acid; HEPE, hydroxyeicosapentaenoic acid; EpDPE, epoxydocosapentaenoic acid; DHDPE, dihydroxydocosapentaenoic acid; HODMA, hydroxydocosahexaenoic acid. Of note, several oxylipins can be formed by different routes as well as by chemical autoxidation.
The effect *APOE4* on brain oxylipins

**Figure 5.** Genotype differences in the ratios of SPMs to their parent compound, EPA or DHA, in cortex of female and male *APOE3* and *APOE4* mice at 2, 9, and 18 mo of age fed a chow diet. Figures of SPMs and their precursors were expressed in μg/mg of tissue to calculate the ratios. Values are means ± SEM; n = 20/group. *P < 0.05, ***P < 0.001.
APOE4 genotype and cognition penetrance affected by sex
APOE4 genotype and cognition penetrance affected by sex
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 Hulley, Andrew Sommerlad, David Ames, Clive Ballard, Sufi Bunejee, Carol Broyne, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Sergi G Costajeda, Amit Dias, Nick Fox, Laura N Griffin, Robert Howard, Helen C Kales, Mika Kivimäki, Eric B Larson, Adeola Ogunsiji, Vasiliki Orgeta, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quercy Sarmus, Los S Schneider, Ger Selbak, Linda Tari, Nashed 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

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
Dementia prevention, intervention, and care

Figure 5: Potential brain mechanisms for preventive strategies in dementia
The Mediterranean Diet

Mediterranean Diet Pyramid

- Meats & sweets
- Poultry, eggs, cheese & yogurt
- Fish & seafood
- Fruits, vegetables, grains (mostly whole), olive oil, beans, nuts, legumes, seeds, herbs & spices

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

• 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
<table>
<thead>
<tr>
<th>Group and Outcome</th>
<th>Relative Risk (95% CI)</th>
<th>% Weight</th>
<th>Reference</th>
<th>n</th>
<th>Study</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive impairment</td>
<td>0.82 (0.59, 1.14)</td>
<td>7.73</td>
<td>Harring et al 2016</td>
<td>6425</td>
<td>WHIMS</td>
<td>aMED</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>0.87 (0.76, 1.00)</td>
<td>13.91</td>
<td>Teugros and Arlesey 2013</td>
<td>17478</td>
<td>REGARDS</td>
<td>MDS</td>
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<tr>
<td>Mild cognitive impairment</td>
<td>0.75 (0.48, 1.22)</td>
<td>4.77</td>
<td>Roberts et al 2010</td>
<td>1141</td>
<td>Rochester Epidemiology Project</td>
<td>MDS</td>
</tr>
<tr>
<td>Mild cognitive impairment</td>
<td>0.72 (0.52, 1.00)</td>
<td>7.79</td>
<td>Scarpace et al 2009</td>
<td>11991</td>
<td>WHICAP III</td>
<td>MDS</td>
</tr>
<tr>
<td>Cognitive decline: MCI or dementia</td>
<td>0.90 (0.72, 1.20)</td>
<td>9.84</td>
<td>Harring et al 2016</td>
<td>6425</td>
<td>WHIMS</td>
<td>aMED</td>
</tr>
<tr>
<td>Cognitive dysfunction: AD, dementia, MCI</td>
<td>0.64 (0.31, 1.31)</td>
<td>2.57</td>
<td>Olsson et al 2015</td>
<td>1058</td>
<td>Uppsala Longitudinal Study</td>
<td>MDS modified</td>
</tr>
<tr>
<td>Change in MMSE (mild)</td>
<td>0.46 (0.25, 0.88)</td>
<td>3.24</td>
<td>Trichopoulos et al 2015</td>
<td>411</td>
<td>EPIC Greece</td>
<td>MDS</td>
</tr>
<tr>
<td>Change in MMSE (substantial)</td>
<td>0.34 (0.13, 0.89)</td>
<td>1.53</td>
<td>Trichopoulos et al 2015</td>
<td>411</td>
<td>EPIC Greece</td>
<td>MDS</td>
</tr>
<tr>
<td>Subjective cognitive function</td>
<td>0.64 (0.35, 0.75)</td>
<td>12.29</td>
<td>Bhushan et al 2018</td>
<td>27942</td>
<td>HPFS</td>
<td>MDS</td>
</tr>
<tr>
<td>Subgroup, DL (I² = 51.6%, p = 0.035)</td>
<td>0.74 (0.64, 0.88)</td>
<td>64.68</td>
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<tr>
<td>Dementia</td>
<td>1.13 (0.79, 1.62)</td>
<td>6.85</td>
<td>Harring et al 2016</td>
<td>6425</td>
<td>WHIMS</td>
<td>aMED</td>
</tr>
<tr>
<td>Probable dementia</td>
<td>0.85 (0.44, 1.68)</td>
<td>3.01</td>
<td>Olsson et al 2015</td>
<td>1058</td>
<td>Uppsala Longitudinal Study</td>
<td>MDS modified</td>
</tr>
<tr>
<td>All-type dementia</td>
<td>0.52 (0.30, 0.91)</td>
<td>3.89</td>
<td>Scarpace et al 2010</td>
<td>409</td>
<td>WHICAP III</td>
<td>MDS</td>
</tr>
<tr>
<td>dementia</td>
<td>0.70 (0.34, 1.45)</td>
<td>2.52</td>
<td>Feart et al 2009</td>
<td>1410</td>
<td>The Three-City</td>
<td>MDS</td>
</tr>
<tr>
<td>Subgroup, DL (I² = 0.9%, p = 0.696)</td>
<td>1.02 (0.78, 1.35)</td>
<td>12.50</td>
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<tr>
<td>Alzheimer disease</td>
<td>0.99 (0.44, 2.24)</td>
<td>2.05</td>
<td>Olsson et al 2015</td>
<td>1058</td>
<td>Uppsala Longitudinal Study</td>
<td>MDS modified</td>
</tr>
<tr>
<td>Alzheimer disease</td>
<td>0.68 (0.42, 1.09)</td>
<td>4.93</td>
<td>Gu et al 2010</td>
<td>1219</td>
<td>WHICAP III</td>
<td>MDS</td>
</tr>
<tr>
<td>Alzheimer disease</td>
<td>0.52 (0.30, 0.91)</td>
<td>3.89</td>
<td>Scarpace et al 2010</td>
<td>409</td>
<td>WHICAP III</td>
<td>MDS</td>
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<td>Feart et al 2009</td>
<td>1410</td>
<td>The Three-City</td>
<td>MDS</td>
</tr>
<tr>
<td>Alzheimer disease</td>
<td>0.60 (0.42, 0.86)</td>
<td>6.91</td>
<td>Scarpace et al 2006</td>
<td>2258</td>
<td>WHICAP III</td>
<td>MDS</td>
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<tr>
<td>Alzheimer disease mortality</td>
<td>0.27 (0.10, 0.71)</td>
<td>1.52</td>
<td>Scarpace et al 2006</td>
<td>182</td>
<td>WHICAP I</td>
<td>MDS</td>
</tr>
<tr>
<td>Subgroup, DL (I² = 0.0%, p = 0.447)</td>
<td>0.61 (0.40, 0.97)</td>
<td>21.82</td>
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<td>Heterogeneity between groups: p = 0.017</td>
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<tr>
<td>Overall, DL (I² = 43.7%, p = 0.025)</td>
<td>0.74 (0.65, 0.84)</td>
<td>100.00</td>
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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 gyriyal 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)
Mediterranean diet adherence is associated with lower dementia risk, independent of genetic predisposition: findings from the UK Biobank prospective cohort study

Oliver M. Shannon, Janice M. Ranson, Sarah Gregory, Helen Macpherson, Catherine Milte, Marleen Lentjes, Angela Mulligan, Claire McEvoy, Alex Griffiths, Jamie Matu, Tom R. Hill, Ashley Adamson, Mario Siervo, Anne Marie Minihane, Graciela Muniz-Terrera, Craig Ritchie, John C. Mathers, David J. Llewellyn and Emma Stevenson

Shannon et al. BMC Medicine (2023) 21:81
https://doi.org/10.1186/s12916-023-02772-3
• No polygenic risk score or APOE genotype * MDP interaction
• No education attainment * MDP interaction
• No one dietary component drove the impact of the MDP

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.
BMJ Open  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, 2 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

UK Nutrition Research Partnership (UK NRP) Collaborative Awards  (NuBrain, 2019-2023)
RESULTS: Neurocognitive Test Battery

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
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).
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, 68% female, baseline year range of 1992–1993, 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
APOE4 affects brain EPA and DHA uptake following intervention

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


Fig. 3 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 23 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 = 0.057). The data were modeled using multivariate linear regression with the change in CSF DHA as the dependent variable and APOE and treatment arm as independent variables. APP amyloid β, 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

- **Birth**
- **Puberty**
- **Fertile Years**
- **Peri Menopause**
- **Menopause**
- **Post Menopause**
- **Death**

- **Estrogen**
- **Progesterone**
Menopause and the menopausal transition (MT)

Birth 44y 51y Death

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

- Concentration
- Memory
- Verbal fluency
- Sleep
- Mood/depression
- Anxiety
Menopause and cognition

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


Scientific Reports | (2021) 11:1686
What is the effect of menopause on cognition, brain fatty acids profiles and synaptic function according to APOE genotype

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

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

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

Matthew G. Pontifex | Anneloes Martinsen | Rasha N. M. Saleh | Glenn Harden | Chris Fox | Michael Müller | David Vauzour | and Anne-Marie Minihane
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)


• Effect of age of HRT use?
• Effect of *APOE* genotype?
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, Michael Hornberger, Craig W. Ritchie, and Anne Marie Minihane

Key findings

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

- 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
Age of HRT initiation (years)

Non-APOE4: standardized $\beta = 0.268$ (p=0.349)

APOE4: standardized $\beta = -0.577$ (p=0.028)

Age of HRT initiation (years)

Non-APOE4: standardized $\beta = 0.310$ (p=0.271)

APOE4: standardized $\beta = -0.555$ (p=0.035)

Saleh et al. Alzheimer’s Research & Therapy, 2023
HRT, APOE, cognition and brain volume
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
CANN Collaborators

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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

Prescribe with caution
- 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
Use this contact information if you have additional questions from today’s webinar.

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Thank you for listening!

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