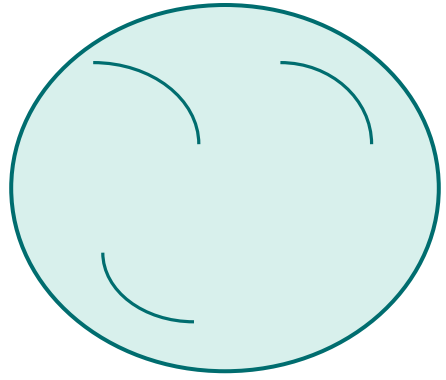
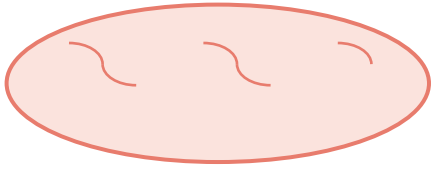
Long-term DHA remodels ApoE4-associated membrane lipids and partially restores mitochondrial homeostasis in the ageing brain



Brain membrane



DHA • Lipid raft • ApoE4



Mitochondrial homeostasis

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Docosahexaenoic acid remodels lipid composition of lipid rafts and mitochondrial function in ApoE4/4 mouse brain: a multi-omic investigation | Molecular Biomedicine | Springer Nature Link: **7**, 212 (2026). https://doi.org/10.1186/s43556-026-00618-x

Precision and personalised nutrition - Oral Presentation

DOCOSAHEXAENOIC ACID REVERSES APOLIPOPROTEIN E4-ASSOCIATED LIPID RAFT DYSFUNCTION AND RESTORES MITOCHONDRIAL HOMEOSTASIS IN THE AGING BRAIN

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Apolipoprotein E4 is the strongest genetic risk factor for late-onset Alzheimer's disease and is associated with disrupted membrane lipid homeostasis, neuroinflammation and mitochondrial dysfunction. This study investigated whether long-term docosahexaenoic acid supplementation remodels brain lipid rafts and restores mitochondrial function in apolipoprotein E4 homozygous mice.

Female apolipoprotein E3 homozygous and apolipoprotein E4 homozygous knock-in mice were fed either a control or docosahexaenoic acid-enriched diet for up to 12 months. Brain lipid raft and non-lipid raft fractions were analysed using integrated lipidomics and proteomics.

Apolipoprotein E4 mice showed a distinct pathological lipid raft signature, characterised by enrichment of sphingomyelin, ceramides and sulfatides, together with increased neuroinflammatory markers. Docosahexaenoic acid supplementation increased omega-3 polyunsaturated fatty acids within lipid rafts, reduced arachidonic acid and attenuated sphingolipid accumulation, with stronger effects in apolipoprotein E4 mice. Multi-omic analysis further showed restoration of mitochondrial pathways related to oxidative phosphorylation and cellular energy metabolism.

These findings suggest that docosahexaenoic acid selectively remodels pathological lipid raft architecture and improves mitochondrial homeostasis in the apolipoprotein E4 brain, supporting precision nutrition strategies for Alzheimer's disease prevention.

Keywords: *Docosahexaenoic acid, Apolipoprotein E4, Lipid rafts, Mitochondrial function, Alzheimer's disease*

Why does Alzheimer's disease (AD) call for precision nutrition?

WHO, 57 million: dementia (2021); 34 million are AD (60-70%)

The same nutritional intervention may not suit every genetic background or disease stage.

Biological heterogeneity of Alzheimer's disease

More than one pathological process

- Aβ and tau, lipid metabolism,
- Neuroinflammation,
- Mitochondria and energy metabolism

The central idea of precision nutrition

From average effects to individual responses

Who benefits?
When intervention?
Through which mechanisms?

Factors that may determine response in this study

- **ApoE4 genotype**
- **Dietary fatty acid: DHA**
- **Ageing or intervention duration**

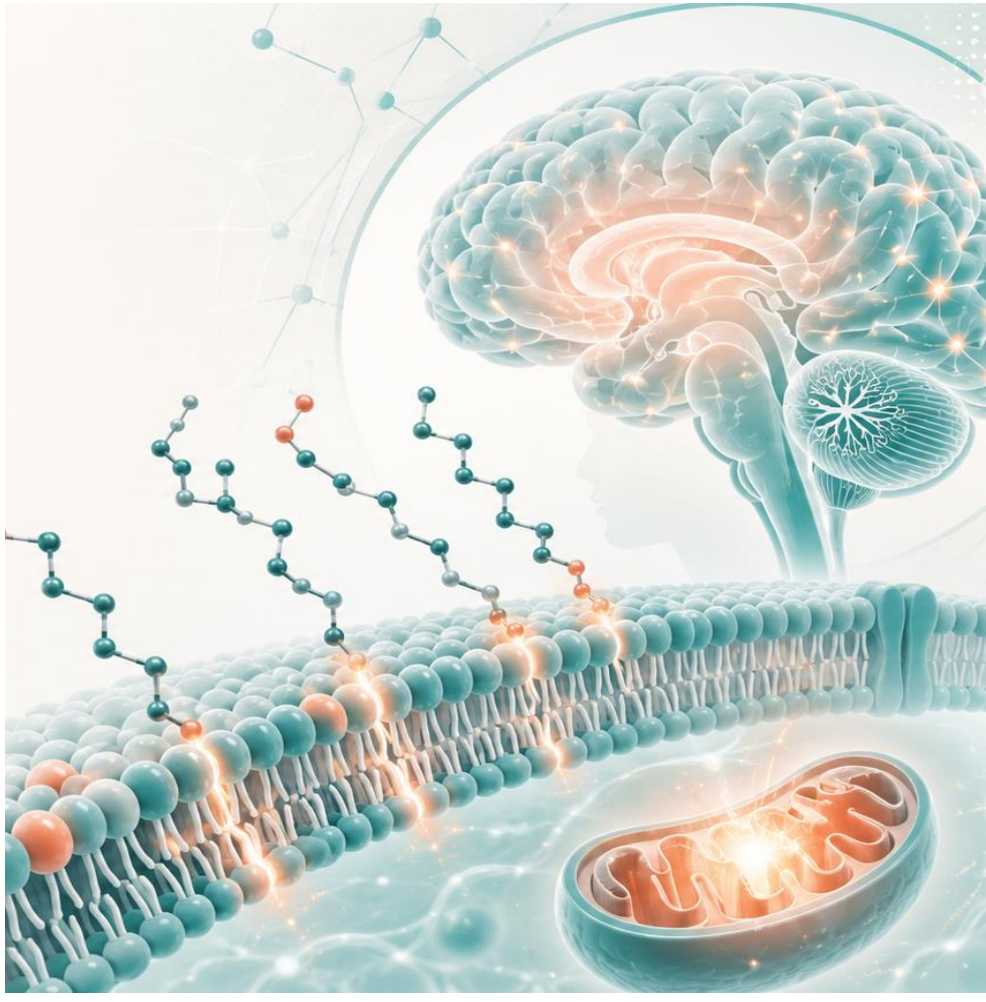
Aβ:amyloid-beta

The key question is not simply whether DHA works, but for whom, when and through which membrane mechanisms.

ApoE genotype × dietary fatty acid × ageing stage = variation in response

Why focus on DHA?

Brain fat is **50% of dried brain** amount



1 A key fatty acid in brain membranes

DHA is the main n-3 polyunsaturated fatty acid in the brain and is abundant in neuronal membranes, synaptic vesicles and lipid rafts.

2 Maintaining membrane fluidity and signal transduction

DHA can affect membrane lipid composition, lipid raft stability, inflammatory signalling and the metabolic environment related to Aβ.

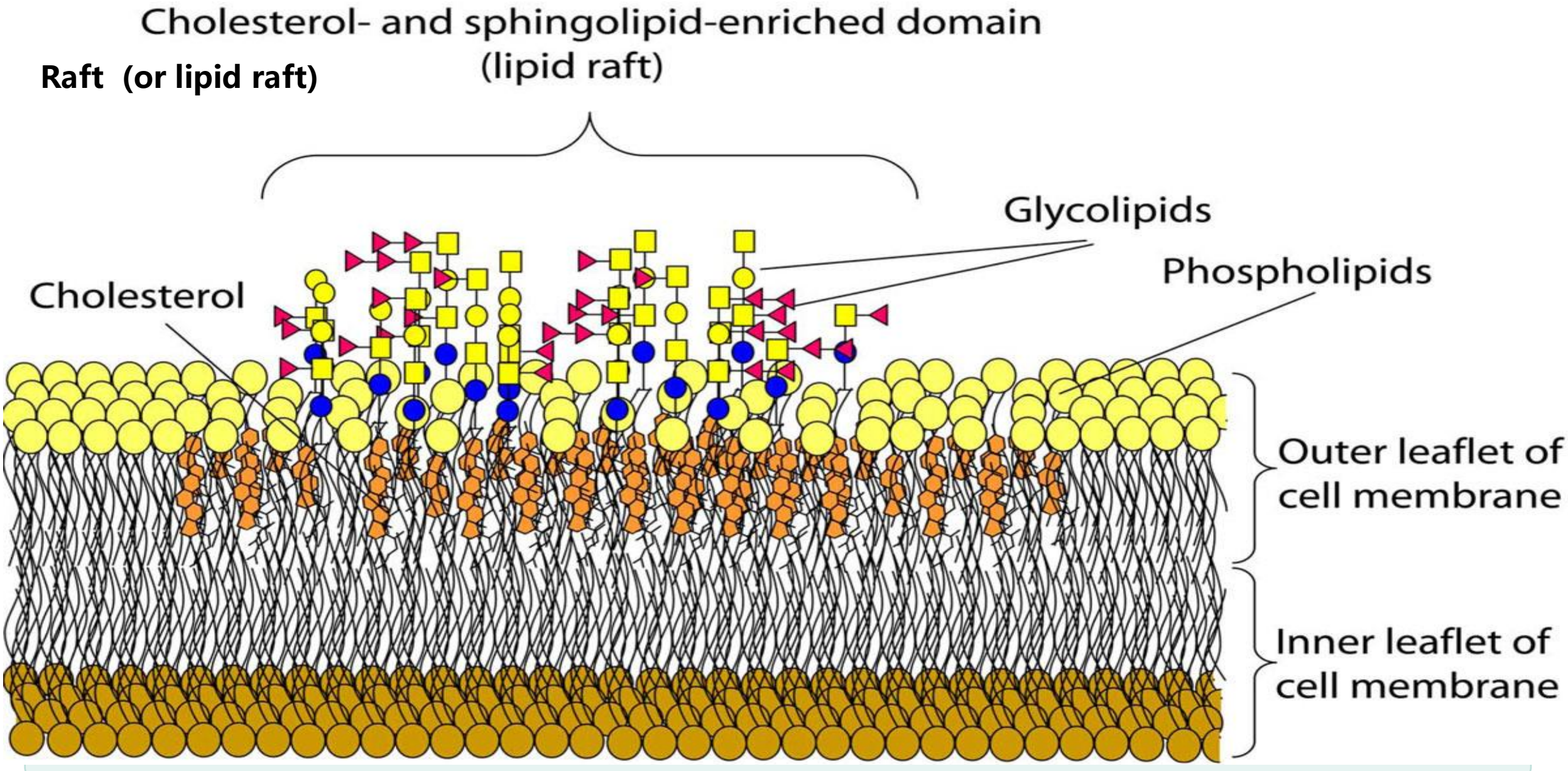
3 Potential for precision nutrition

Endogenous synthesis is limited, making dietary intake relevant..

The central research question

Can long-term DHA remodel lipid rafts in the ApoE4 background and improve neuroinflammation and mitochondrial homeostasis?

Raft (or lipid raft)



Experimental design and multi-omics workflow

Apolipoprotein E3 (ApoE3): a major isoform of the ApoE protein that plays a **crucial role in lipid and neuronal homeostasis**
APOE4 is also associated with greater **neuroinflammation** and reduced ability to maintain healthy blood vessels in the brain

Genotype, diet and time → behavioural testing → tissue collection → lipid raft and multi-omics analyses

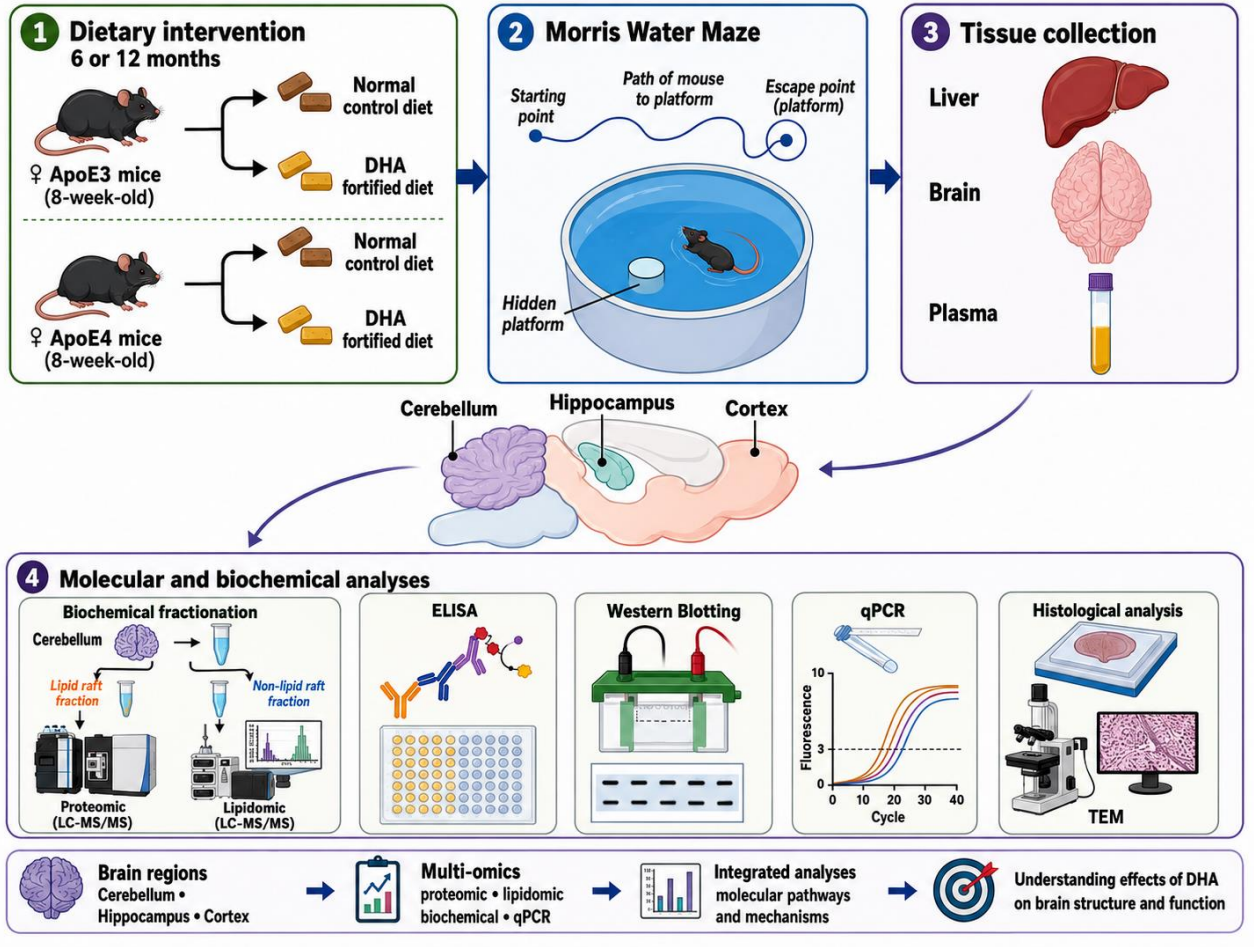
CONTROL DIET	DHA-ENRICHED DIET
ApoE3/3 + control	ApoE3/3 + DHA
ApoE4/4 + control	ApoE4/4 + DHA

EXPOSURE

Long-term feeding, with study time points at 6 and 12 months (up to 12 months).

BRAIN ANALYSIS

Lipid raft and non-raft fractions analysed by integrated lipidomics and proteomics.



Main results (1):

Behaviour and classical Alzheimer's-related markers

This model is closer to an early metabolic and inflammatory stage than to a typical Alzheimer's model with clear cognitive impairment.

01 Behavioural findings

Escape latency fell during Morris water maze training, showing that mice learned the task. Platform crossings showed no clear group differences.

02 Aβ/APP (amyloid precursor protein)/IDE (insulin-degrading enzyme)/p-Tau (phosphorylated Tau)

Classical Alzheimer's-related markers changed modestly, without prominent Aβ or tau pathology.

03 Interpretation

The later lipidomic and proteomic findings may therefore reflect early changes in membrane lipids, neuroinflammation and mitochondrial homeostasis.

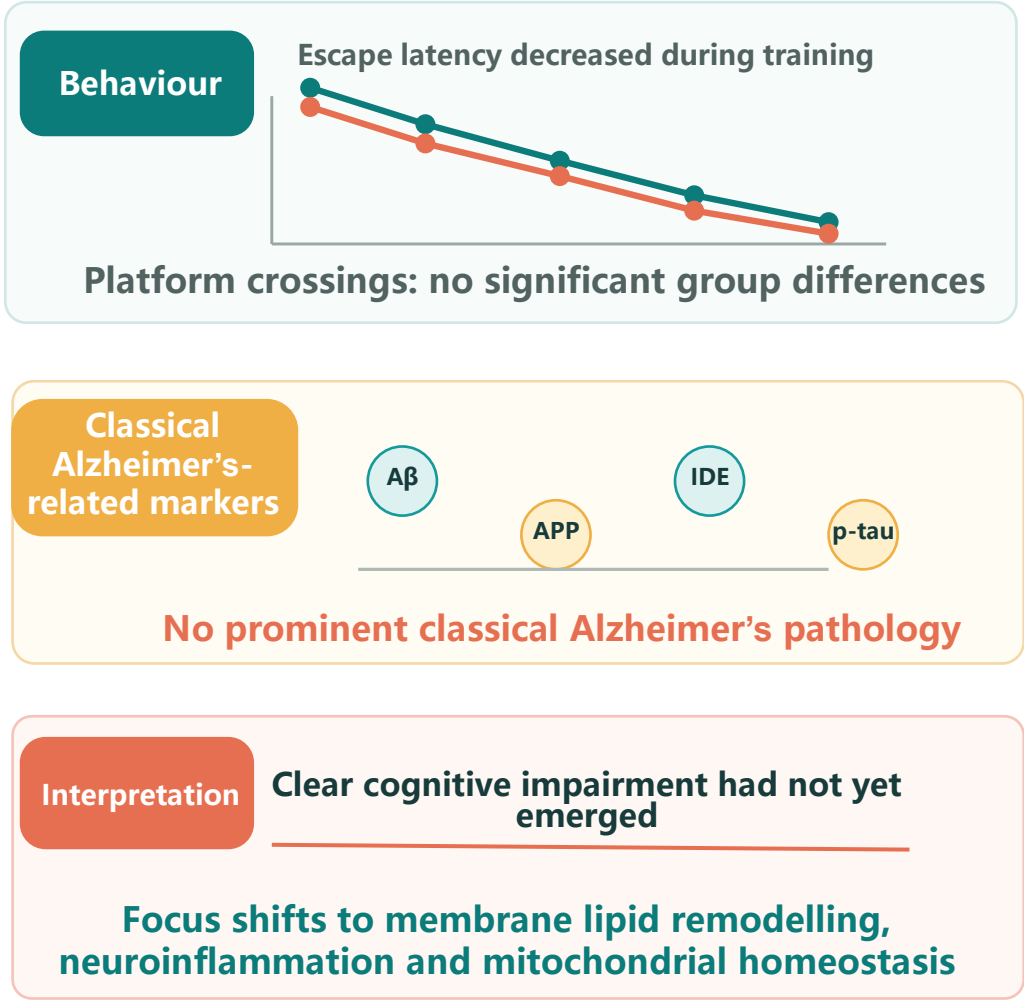


Figure 1. Phenotype and classical Alzheimer's-related markers

Main results (2)

ApoE4 increases neuronal vulnerability and neuroinflammation

Compared with ApoE3 mice, ApoE4 mice showed greater neuronal vulnerability and glial activation. Long-term DHA partly reduced ApoE4-associated cortical inflammation.

01 **Nissl-positive neurons**

ApoE4 mice had a lower proportion of Nissl-positive neurons in the cortex and hippocampal CA1, suggesting increased early neuronal vulnerability.

02 **GFAP, Glial Fibrillary Acidic Protein: astrocytes**

Higher GFAP indicates astrocyte activation, which was more evident with ageing in the ApoE4 background.

03 **Iba (ionized calcium binding adaptor molecule)1: microglia**

Higher Iba1 indicates inflammation and microglial activation. At 12 months, DHA reduced cortical inflammatory signals in ApoE4 mice.

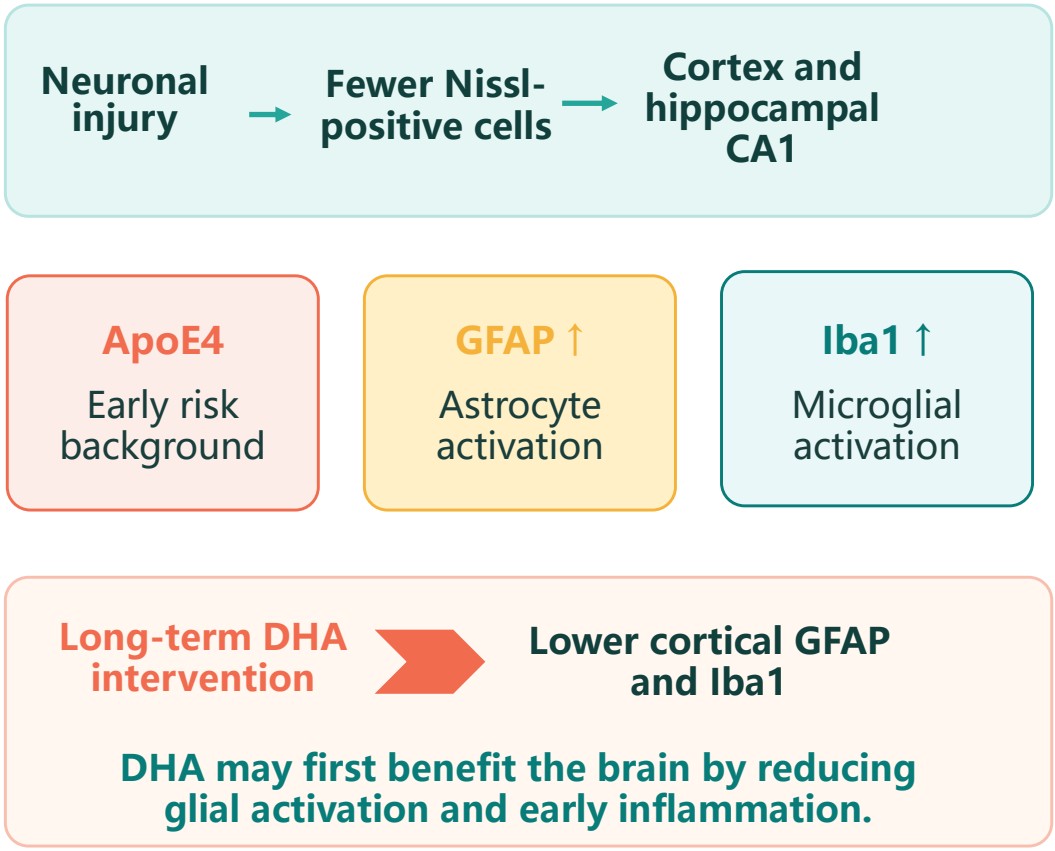


Figure 2. Neuronal and neuroinflammatory markers

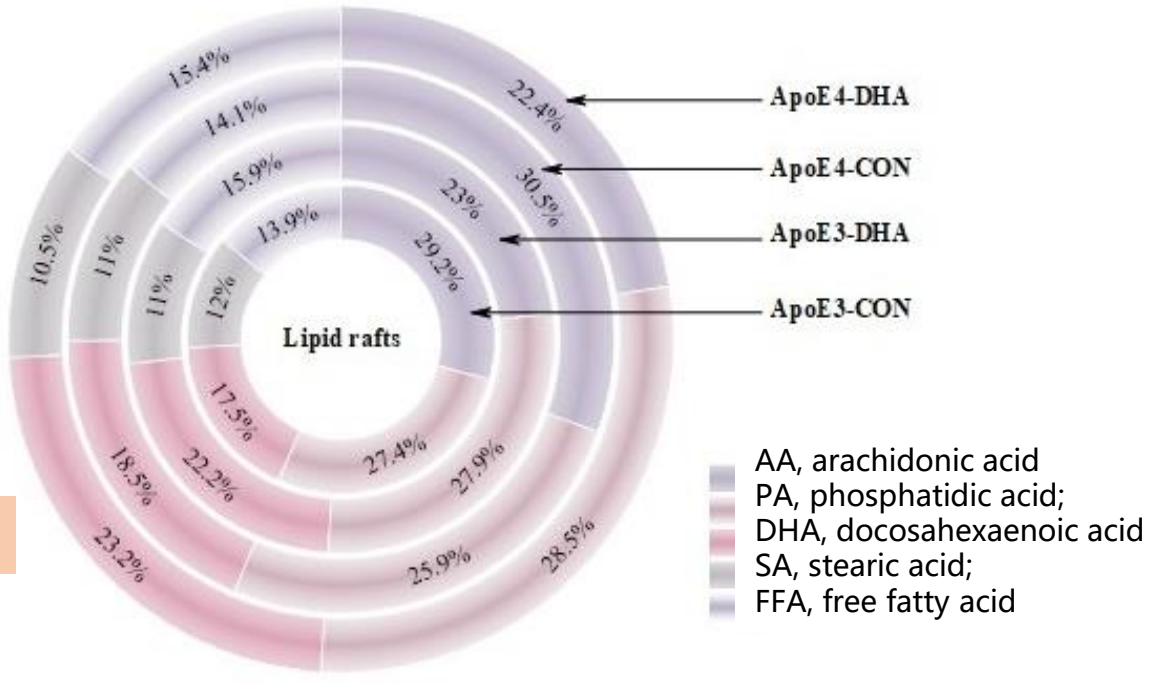
Focus on early neuroinflammation and histological changes rather than claiming cognitive improvement.

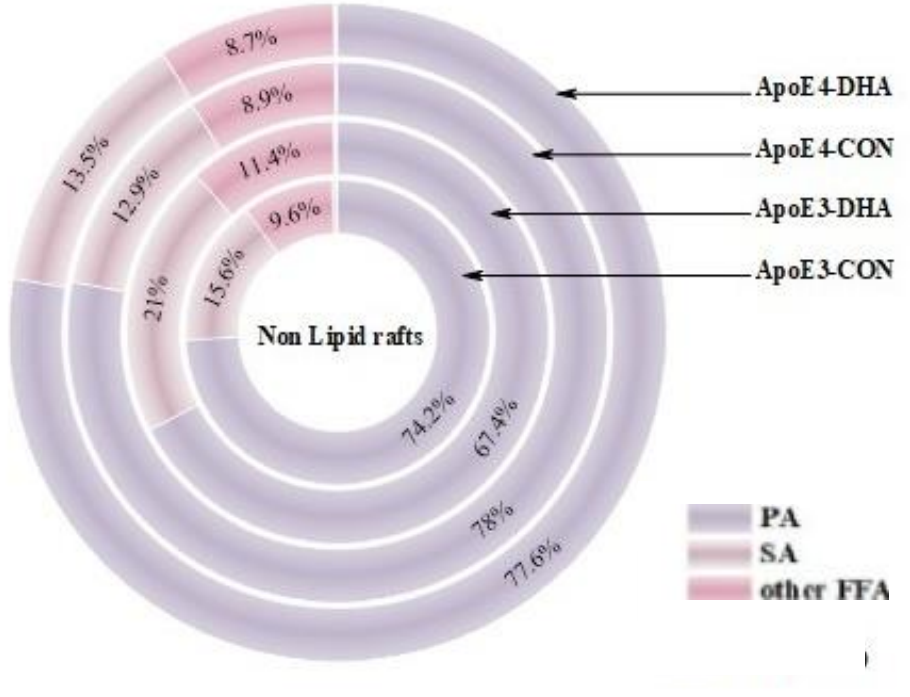
Main results (3) by lipidomic assay

Lipid rafts and non-raft regions have different lipid architectures

Rafts, high in DHA, AA, n-3 PUFA and cholesterol; non-raft, more saturated fatty acids, phospholipids.

DHA





● (Lipid) raft

⬢ Non-raft region

DHA does more than add fatty acids to the diet; it remodels the lipid environment of specific membrane

Lipidomics results summary

ApoE4 is associated with a distinct lipid-raft signature

Raft and non-raft fractions differed in both control genotypes.

DIFFERENTIAL LIPIDS: RAFT VERSUS NON-RAFT

374

ApoE3 control mice

differential lipids between fractions

450

ApoE4 control mice

differential lipids between fractions

These counts describe differential lipids in lipid raft-versus-non-raft comparisons in control mice—not the number of lipids changed by DHA.

APOE4 CONTROL RAFTS

Higher abundance of three sphingolipid classes

SM	Sphingomyelin
Cer	Ceramides
SL	Sulfatides

INFLAMMATORY CONTEXT

Neuroinflammatory markers were also increased in ApoE4 mice (Figure 2).

ApoE4 combines a distinct raft lipid profile with a higher inflammatory signal.

TREATMENT RESPONSE · COMPARTMENT-SPECIFIC

DHA remodels the lipid balance within rafts in ApoE4

DHA shifted the raft lipid profile, with a stronger remodelling effect in ApoE4 mice.

ABBREVIATIONS

PUFA = polyunsaturated fatty acid
AA = arachidonic acid

DIRECTION OF CHANGE WITH DHA

Omega-3 PUFA in rafts	**INCREASED**
Arachidonic acid in rafts	**DECREASED**
Sphingolipid accumulation	**ATTENUATED**

The remodelling effect was stronger in ApoE4 mice.

DHA mainly redistributed lipids across compartments rather than simply adding omega-3 fatty acids.

INTEGRATED INTERPRETATION · BRIDGE TO PROTEOMICS

Lipidomics links the changes to three connected pathways

DHA affected lipid networks across membrane compartments, with more selective effects in ApoE4.

ABBREVIATIONS

TAG = triacylglycerol | DAG = diacylglycerol | CE = cholesteryl ester
PC = phosphatidylcholine | PE = phosphatidylethanolamine | PI = phosphatidylinositol
PS = phosphatidylserine | CL = cardiolipin | Cer = ceramide | SM = sphingomyelin | SL = sulfatide

1 Neutral-lipid turnover

TAG · DAG · CE

After DHA, raft TAG decreased, while DAG and CE were reorganised.

Signals altered lipid movement between droplets and membranes.

2 Sphingolipid balance

Cer · SM · SL

ApoE4 rafts showed higher sphingolipids. DHA attenuated accumulation and shifted ceramide across compartments.

The ApoE4 sphingolipid environment was particularly responsive.

3 Membrane lipids & mitochondria

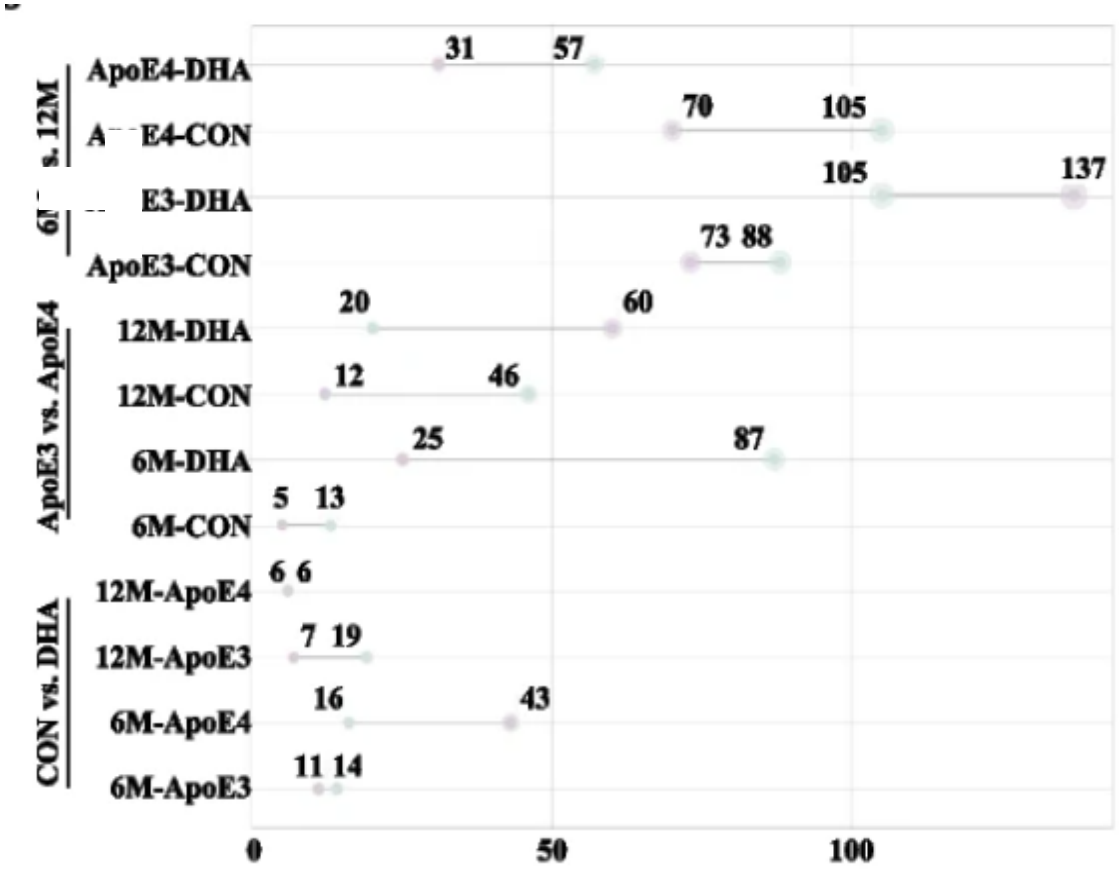
PC · PE · PI · PS · CL

ApoE4 had lower CL. DHA increased CL and PE and remodelled PC, PI and PS.

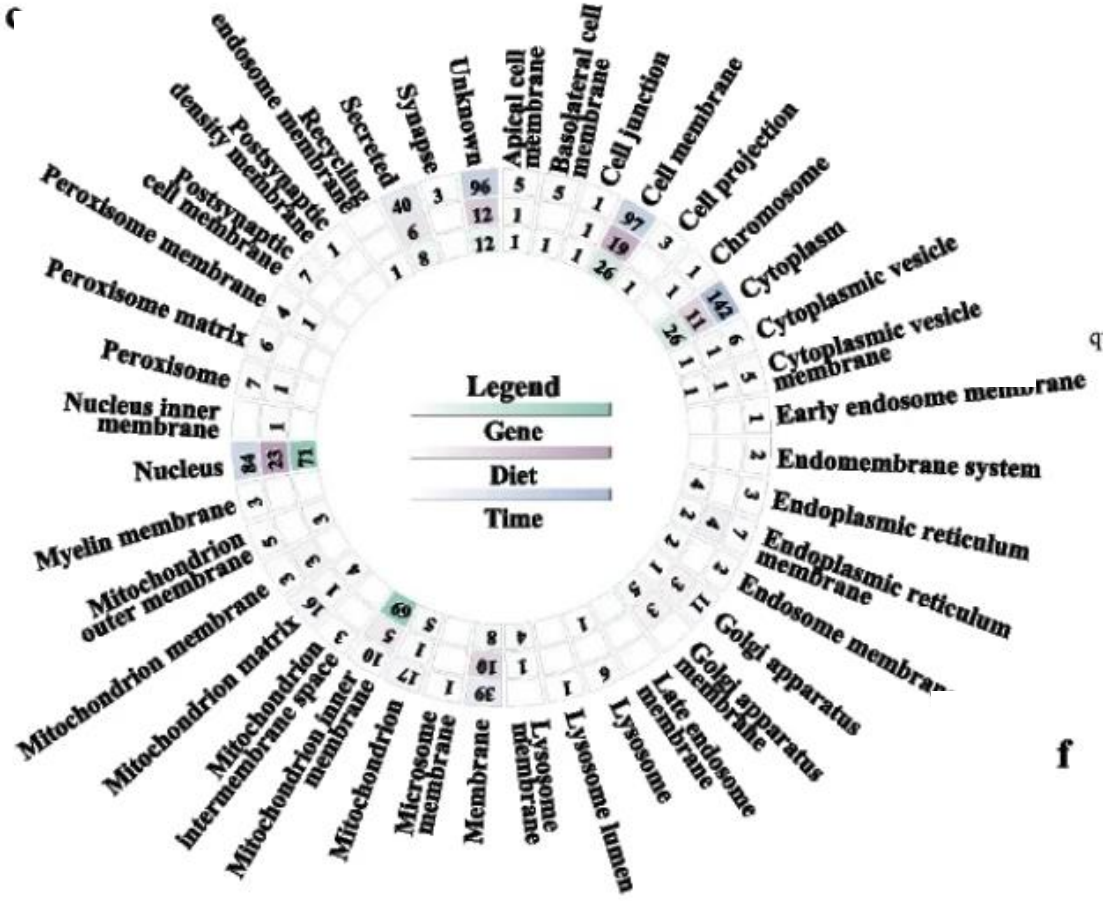
These lipid changes connect membrane structure with mitochondrial biology.

Together, the lipidomics points to membrane remodelling; the next slide adds proteomic evidence for mitochondrial energy metabolism.

Main results (4) by proteomic assay



A. The number of upregulated and downregulated differentially expressed proteins among intergroups



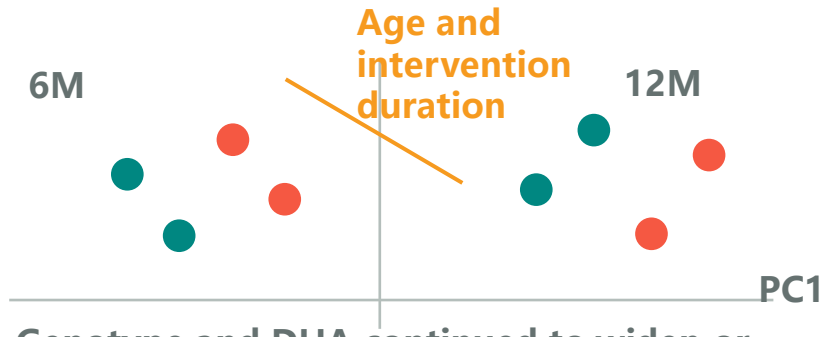
B. Integrating subcellular localization patterns of proteins differentially regulated by genotype, diet, and intervention duration

Proteomics: ApoE4 effects converge on mitochondrial energy metabolism

Proteomics showed a clear overall pattern:

Over time, ApoE genotype and DHA jointly shaped the lipid raft proteome. The most prominent functional changes involved mitochondria and energy metabolism.

PCA: time accounted for the greatest variation



Genotype and DHA continued to widen or narrow group differences at each time point.

Key point DHA generally reduced proteomic differences in ApoE4, suggesting partial normalisation.

Functional enrichment: different levels converge on energy metabolism

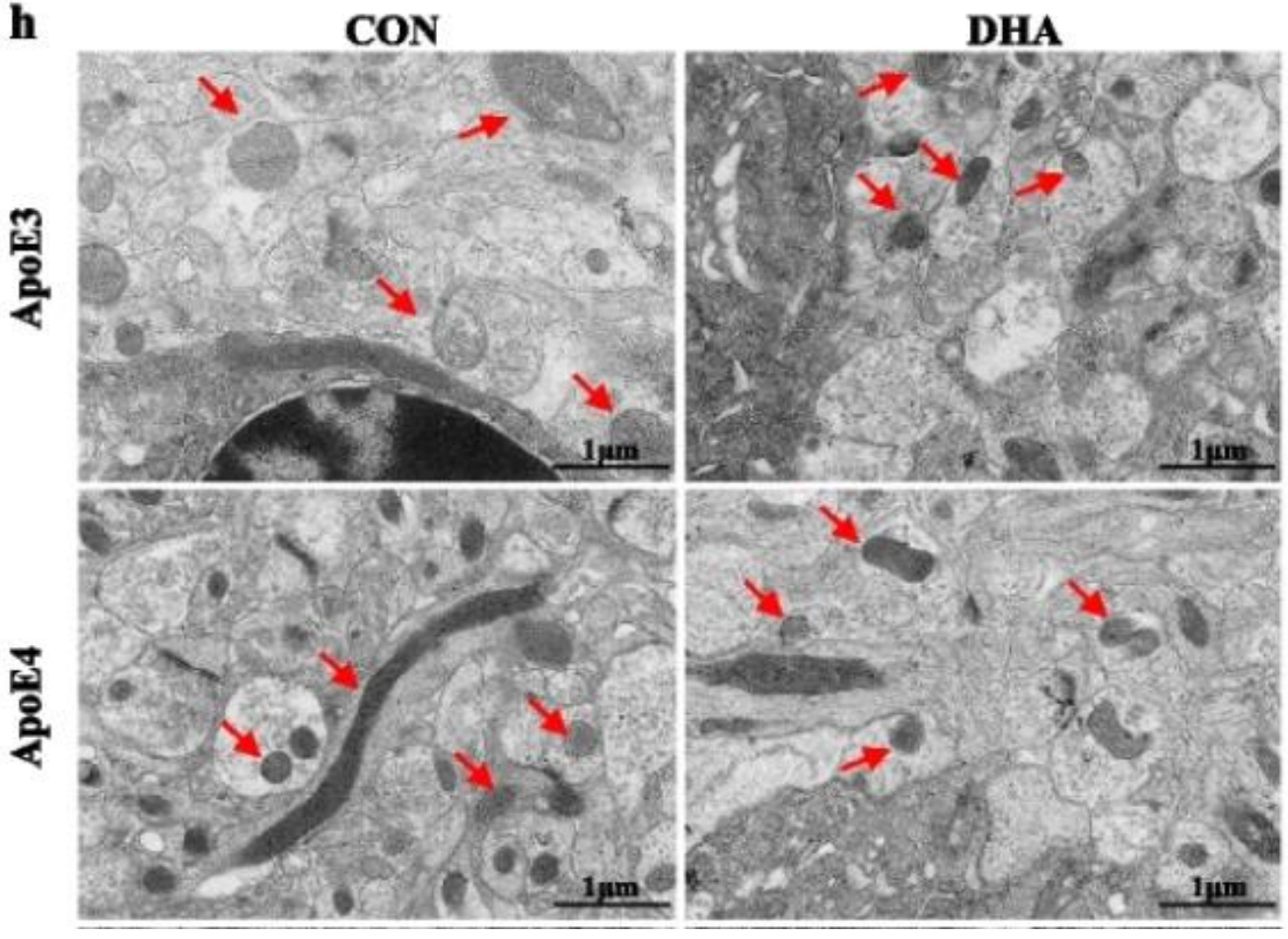
ApoE genotype × DHA × time

RNA processing	Core metabolism	Mitochondria
Spliceosome	Glycolysis	OXPHOS
mRNA surveillance	Pyruvate	Respiratory chain
Early group differences	Marked remodelling with ApoE4 plus DHA	Genotype differences were especially clear at 12 months.

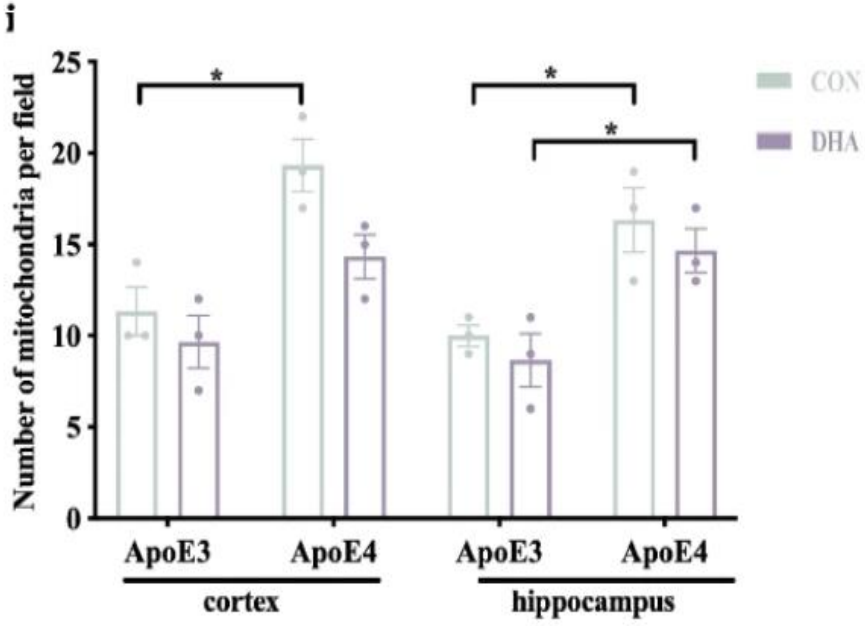
Mitochondrial bioenergetic imbalance

Long-term ApoE4 expression impaired oxidative phosphorylation and energy homeostasis. DHA partly restored them.

Main results (5) by mitochondrial homeostasis assay



Transmission electron microscopy images of mitochondria (red arrows) in the cerebral cortex of mice, with "Nuc" indicating nucleus.



Quantitative analysis of the number of mitochondria per field in the cerebral cortex and hippocampus, *N* = 3, mean ± SEM.

From lipid raft remodelling to mitochondrial homeostasis: an integrated model of ApoE4 and DHA

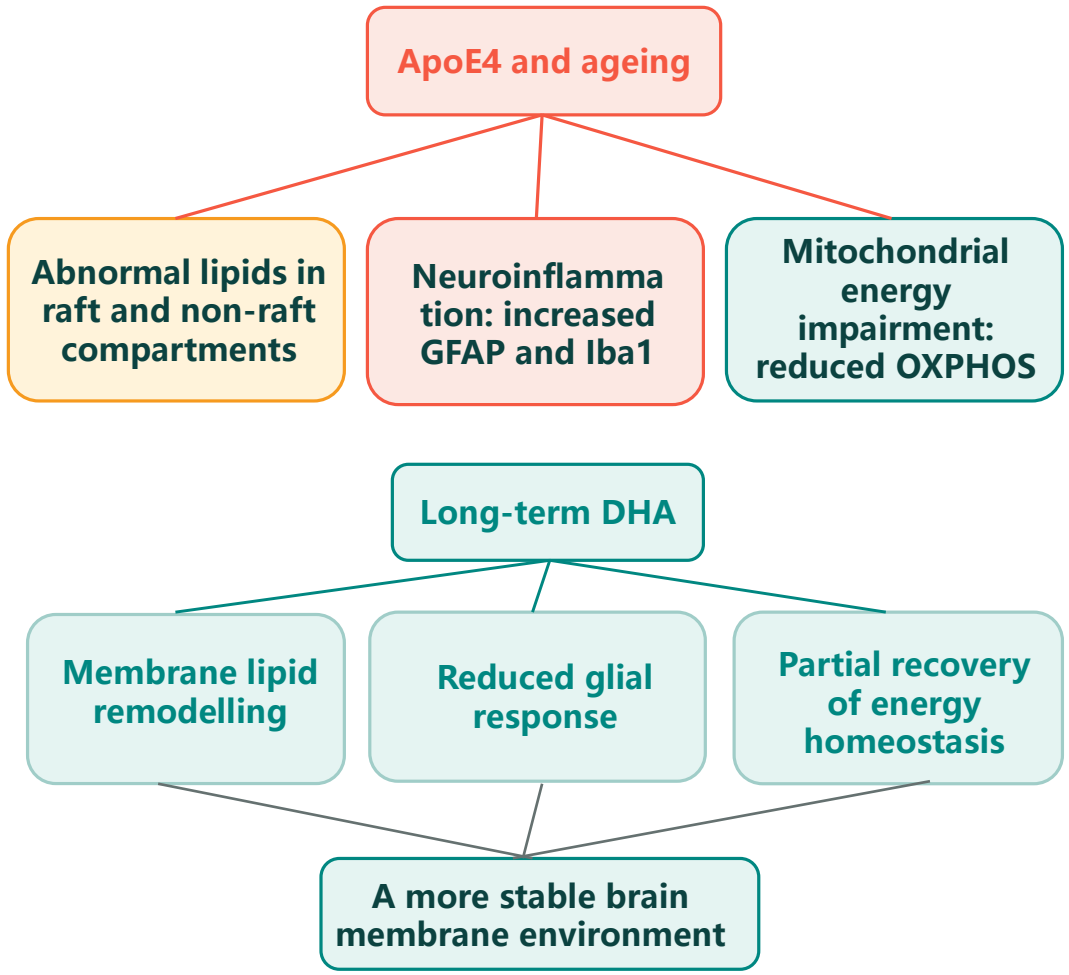
Transmission electron microscopy adds further evidence:

ApoE4 neurons did not necessarily show the most obvious structural damage. They may first enter a state of compensatory mitochondrial stress.



Interpretation ApoE4 may maintain energy supply by increasing mitochondrial number, while quality control and oxidative phosphorylation remain impaired.

Working model



DHA may act mainly during early metabolic and inflammatory stages, rather than directly reversing established Aβ or tau pathology.

Conclusion: towards genotype-specific precision nutrition

Three take-home messages

01

ApoE4 first shows an early metabolic phenotype

Lipid raft, inflammatory and mitochondrial abnormalities were already present before clear cognitive impairment and mature Aβ or tau pathology.

02

DHA mainly remodelled lipids rather than simply adding more

Long-term DHA changed lipid distribution across raft and non-raft fractions, lipid turnover, and some aspects of glial and mitochondrial homeostasis.

03

Nutritional response depends on genotype, time and membrane compartment

ApoE3 and ApoE4 responded differently to the same DHA intervention, supporting future genotype-specific nutrition strategies.

Next step: from animal mechanisms to human validation

Current evidence	→	Questions for future research
Female ApoE3/3 and ApoE4/4 knock-in mice		Human and clinical studies
Long-term interventions for 6 or 12 months		A clearer dose and formulation of DHA
Lipidomics, proteomics and TEM		Causal multi-omics mechanisms

Implications for precision nutrition

The question should extend beyond: "Does DHA work?"

It should also ask: "For whom, when and in what form does it work best?"

Thank you!

Questions?

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molecules

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