Fish oil supplementation increases cerebrovascular responsiveness in women

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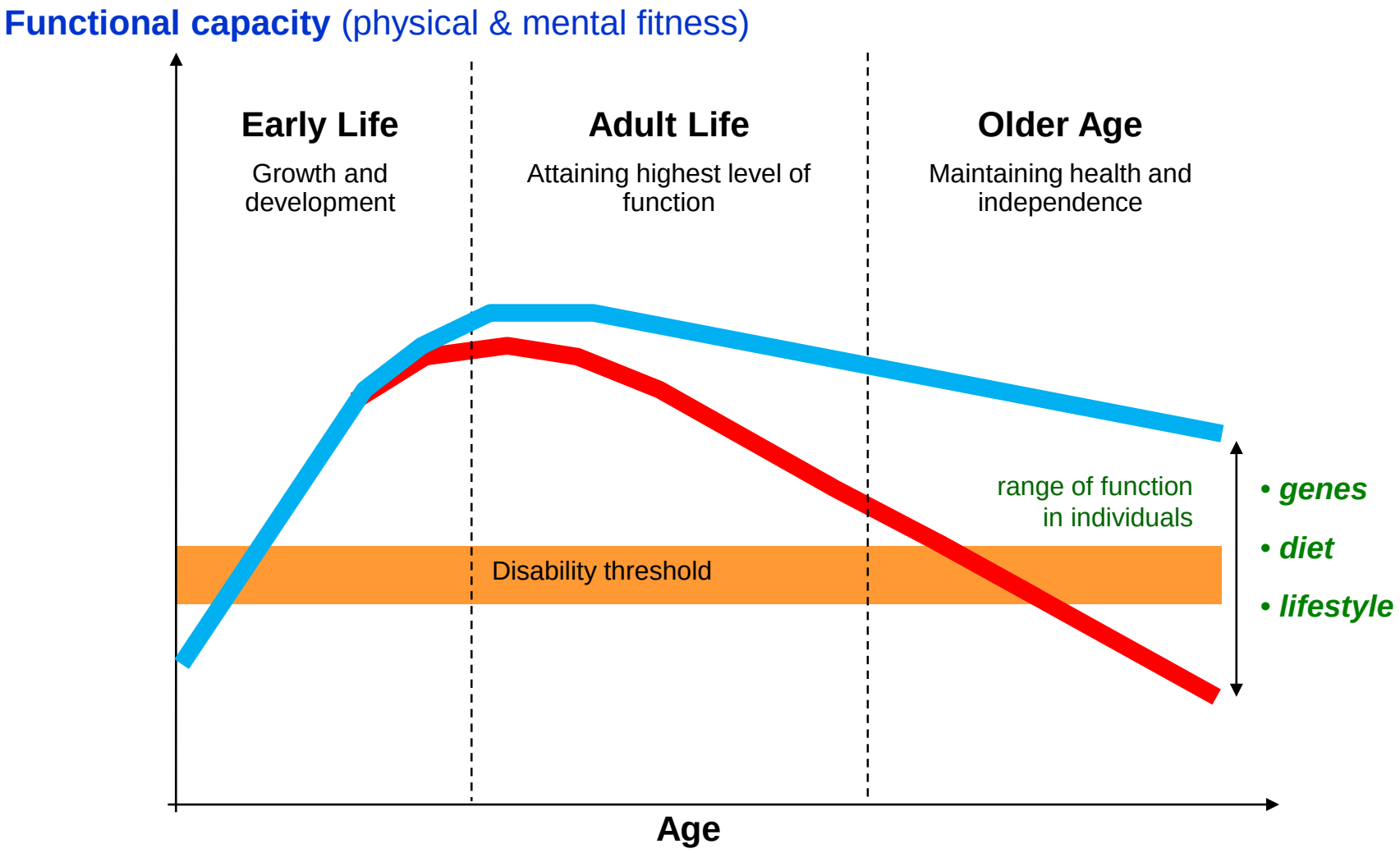
CLINICAL NUTRITION RESEARCH CENTRE

Preventive Health for an Aging Population



Adapted from WHO/HPS Geneva, 2000

Potential Health Benefits of Long Chain Omega-3 PUFA

Enhancing early infant development & growth
Promoting fitness (physical, mental, reproductive)
Counteracting chronic disease (prevention, treatment)

Cardio-metabolic

blood lipids (TG↓ HDL↑)
blood pressure
arterial compliance
endothelial dilatation
platelet aggregation
heart rate
heart rate variability
arrhythmia, sudden death
ischemic heart disease
heart failure
kidney damage
stroke

abdominal adiposity
insulin resistance, diabetes

Inflammatory

psoriasis/dermatitis
rheumatoid arthritis
inflammatory bowel disease
immune renal disease
periodontal disease
osteoporosis?
asthma?
COPD?

Cancer?

Behavioural

depression, bipolar disorder
cognitive impairment, ADHD
schizophrenia? autism?

Clinical trial evidence is still limited

Need to determine optimal dose and formulation (EPA and/or DHA) for each indication

Effects of initial omega-3 status, gender, genetic variation, pregnancy, etc. must be considered

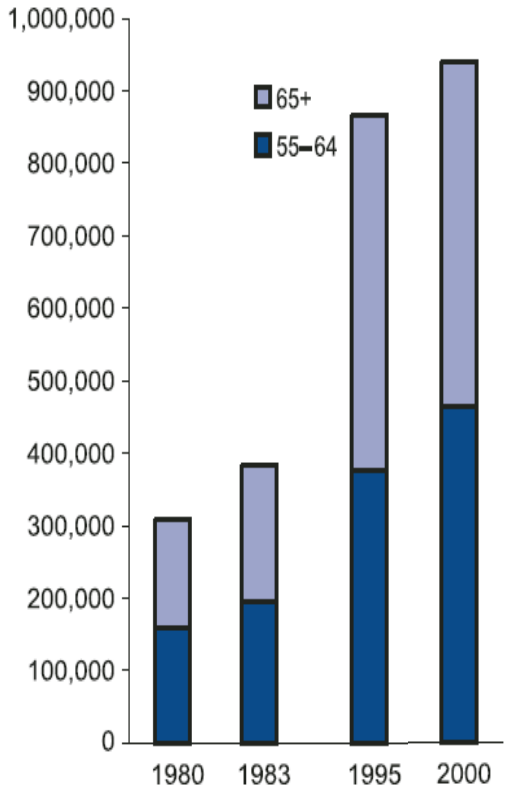
e.g. we have reported differences between men and women in relationships of omega-3 intake to platelet aggregation and adiposity

Obesity and the metabolic syndrome – impacts on health

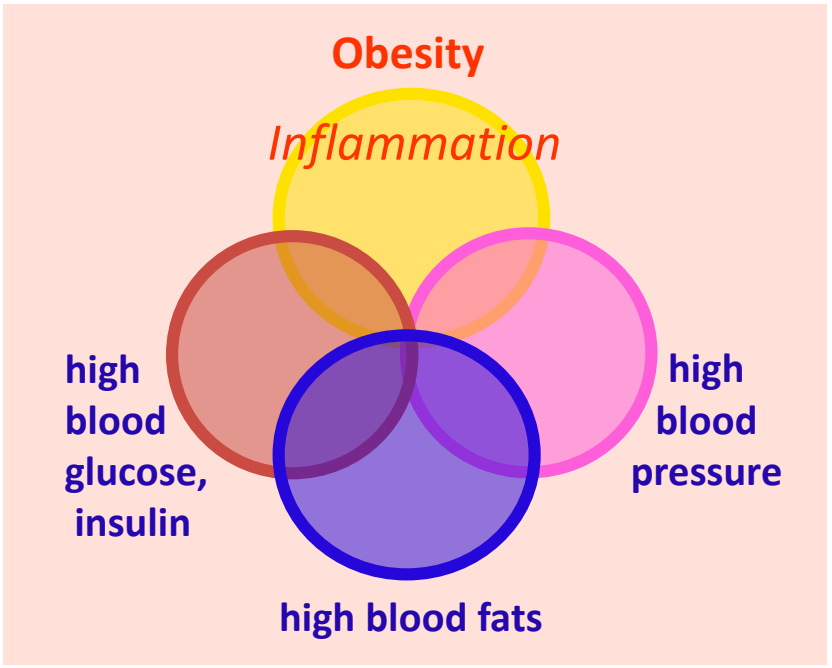
↑ obesity

Metabolic Syndrome

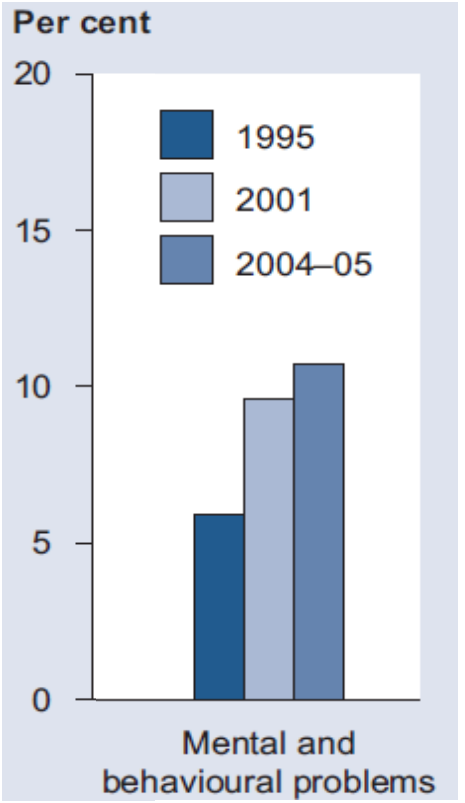
↓ mental fitness



Prevalence of obesity in older Australians
AIHW, 2005



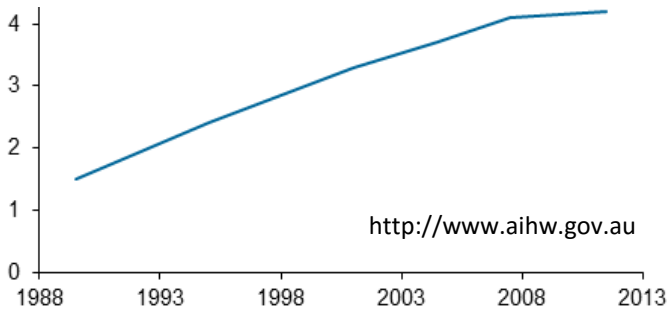
predisposes to heart disease, diabetes
chronic inflammatory disorders



Prevalence of self-reported mental disorders
AIHW, 2008

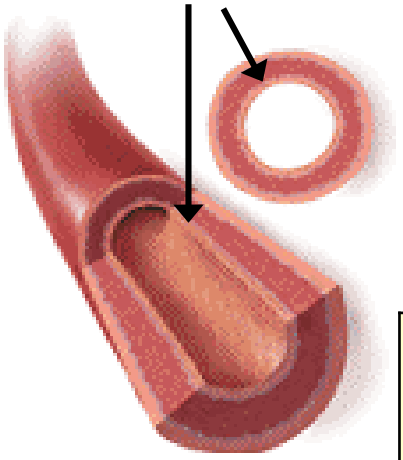
%

Prevalence of diabetes in Australia

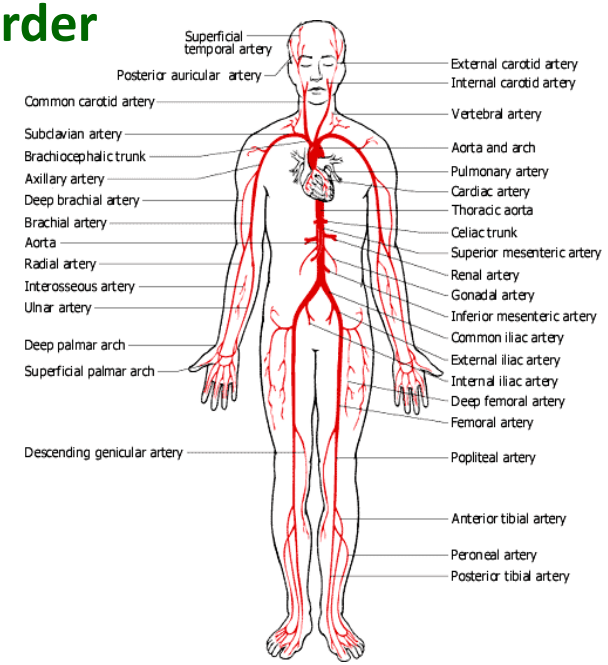


Metabolic syndrome is a circulatory disorder

healthy endothelium



- regulates vasomotor tone
- inhibits cell adhesion, platelet aggregation
- capillary functions (selective permeability)
- integrity of vessel wall (counteracts hypertrophy)

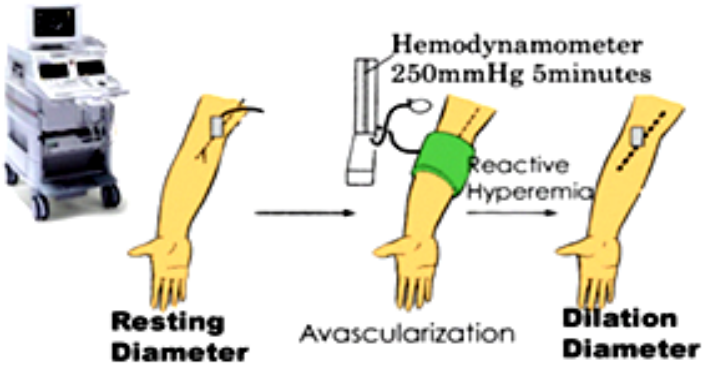


endothelial secretory/expression products

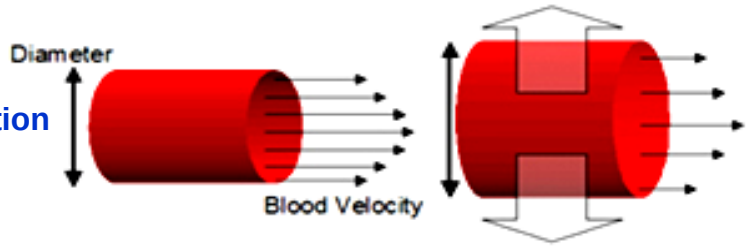
P Grammas *J Neuroinflamm* 2011

Extracellular matrix factors	***Proteases***
Fibronectin, laminin	Thrombin
collagen I, II, III, IV, VIII, XVIII	MMPs
proteoglycans	tPA
Anti- and pro-coagulation factors	***Growth factors***
PGI_2	PDGF
thrombomodulin	EDGF
AT III	FGF
heparin sulfate	IGF
vWF	TGF-β
TXA_2	GM-CSF
thromboplastin	G-CSF
Factor V	***Vasorelaxation factors***
PAF	NO
PAI-1, PAI-2	PGI_2/E_2
Inflammatory Chemokines and Cytokines	EDHF
IL-1, IL-6, IL-8	***Vasoconstriction factors***
LTB_4, C_4, D_4, E_4	TXA_2/F_{2a}
MCP-1, MCP-2	EDCF
MHC II	Endothelin
Cell Adhesion Molecules	Leukotrienes
	free radicals

Non-invasive assessment of endothelial function

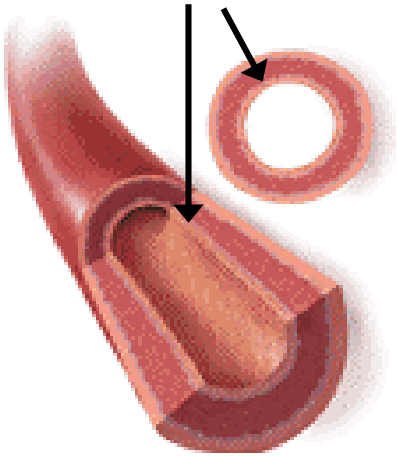


Flow mediated dilatation (FMD)



Negative impact of diet/lifestyle on the circulation

healthy endothelium



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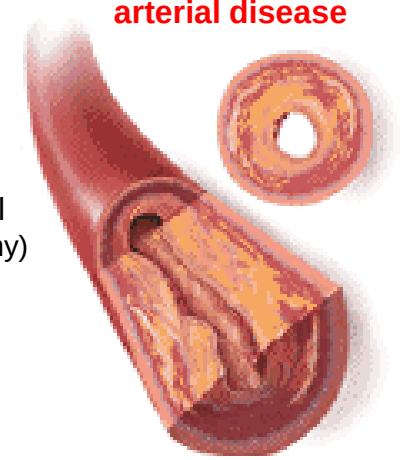
arterial disease

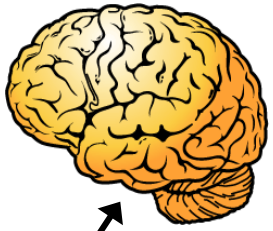


Obesity
High blood pressure
High blood sugar
High blood fat
High salt intake
Smoking

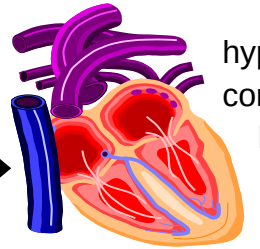
endothelial dysfunction

- impaired vasodilatation *(early)*
- pro-thrombotic and inflammatory mediators (thromboxane, cytokines, adhesion molecules, etc)
- Increased arterial stiffness due to vascular remodelling and hypertrophy *(long term)*

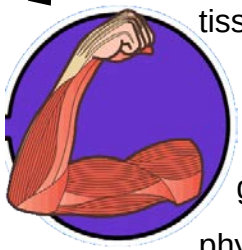
impaired blood flow



cognitive decline
depression
neurodegenerative disorders

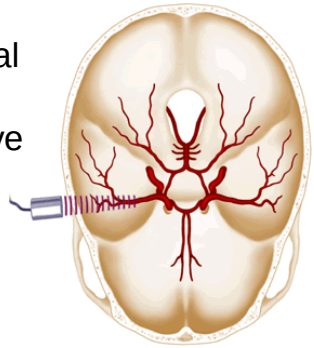


hypertension
coronary disease
heart failure
stroke
renal disease

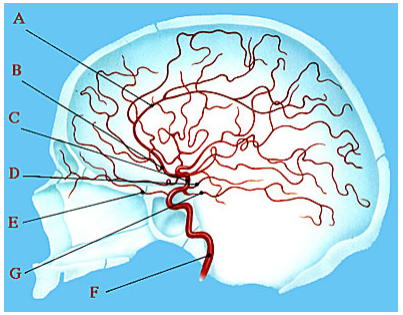


tissue inflammation
insulin resistance
impaired fat, glucose metabolism
physical incapacity

We can measure blood flow velocity in cerebral arteries by Transcranial Doppler Ultrasound (TCD). It is reduced in adults with mild cognitive impairment. Sun Z et al Eur J Neurol 2007



A: Pericallosal Artery
B: **Anterior Cerebral Artery**
C: **Middle Cerebral Artery**
D: Anterior Choroidal Artery
E: Ophthalmic Artery
F: Internal Carotid Artery
G: Posterior Cerebral Artery

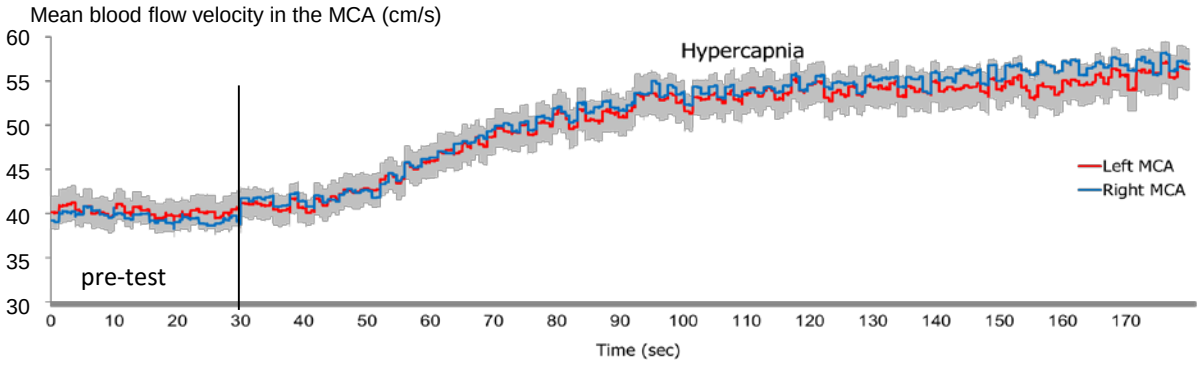


TCD assessment of cerebrovascular function

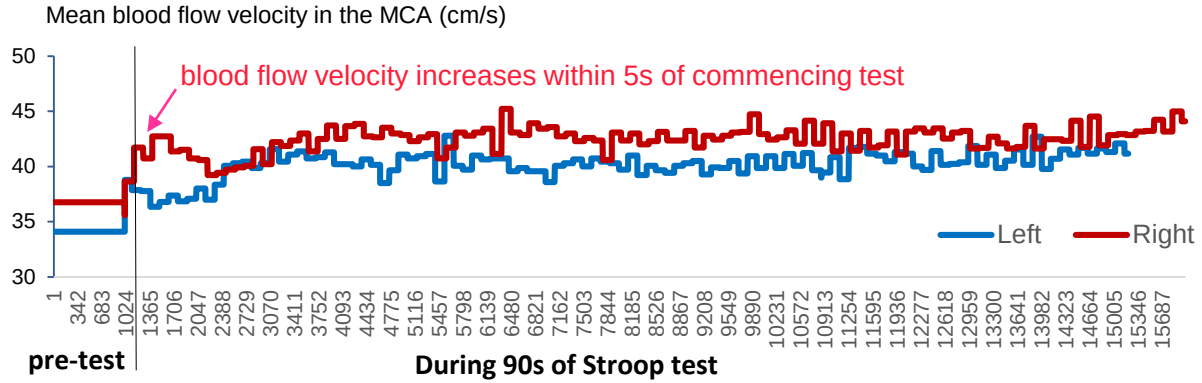
Continuous transcranial Doppler (TCD) ultrasound monitoring of blood flow velocity in the middle cerebral artery (MCA)

Bilateral probes are used for steady state assessment of mean blood flow velocity and pulsatility index (arterial stiffness) and for dynamic assessment of cerebrovascular responsiveness (CVR) to hypercapnia or to mental tasks.

Global vasodilatation with CO2 challenge (CVR to hypercapnia)



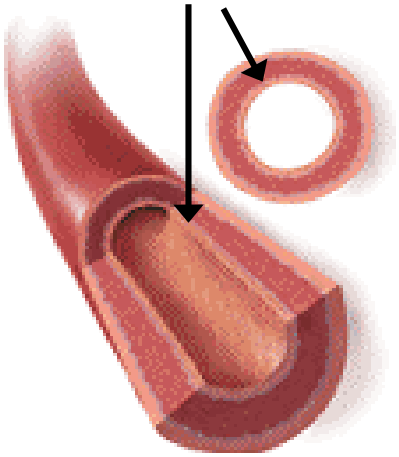
Regional vasodilatation during performance of a cognitive task



CVR is maximum increase in blood flow velocity, expressed as % of baseline

Positive impact of diet/lifestyle on the circulation

healthy endothelium



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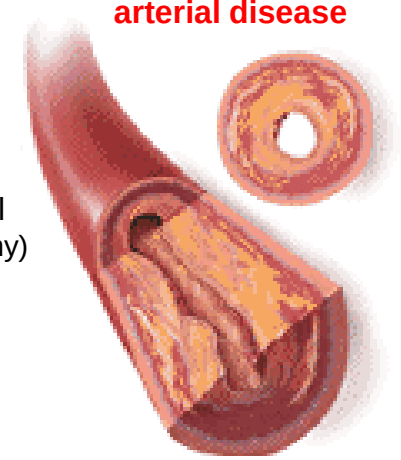
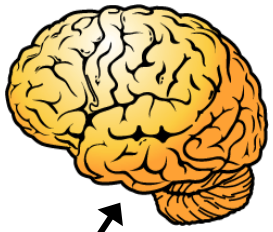


impaired blood flow



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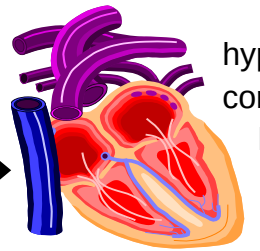

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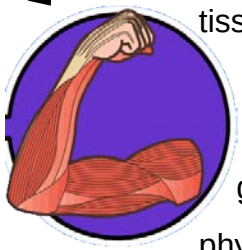

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endothelial dysfunction

- impaired vasodilatation *(early)*
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Can be prevented or improved by regular aerobic exercise and supplementation with selected bioactive *(vasoactive)* nutrients

Several vasoactive ingredients have been shown to improve FMD, cognition and cerebrovascular responsiveness

- cocoa flavanols
- wild green oat extract (Neuravena)
- resveratrol

Omega-3 PUFA can act via multiple endothelial mechanisms to improve FMD and arterial compliance.

Can Omega-3 PUFA also enhance cerebrovascular function?

Bioscience Hypotheses (2008) 1, 103–108

Mental health benefits of omega-3 fatty acids may be mediated by improvements in cerebral vascular function☆

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KEYWORDS
Omega-3 fatty acids;
Cerebral blood flow;
Blood-brain barrier;
Endothelium;
Psychiatric illness

Abstract Since the pivotal role of long chain omega-3 (n-3) polyunsaturated fatty acids (PUFA) in brain structure and development became apparent in the 1970s, these lipids have been investigated in relation to a range of psychiatric disorders, with some positive and some conflicting evidence to support their use as a supplementary treatment for various symptoms. A number of mechanisms of action have been proposed to account for their potential benefits, largely based on their structural role in brain development and purported influences on central neurotransmission.

Theories on the pathogenesis of mental health and psychiatric illness have traditionally focused on the role of neurotransmitters, although there is also ample evidence that psychiatric disorders are associated with impaired cerebral blood flow (CBF) or impairments in blood-brain barrier (BBB) function. Associations between cardiovascular and psychiatric pathologies are further indicative of a possible underlying vascular component to psychiatric illness. We hypothesise that treatment with vasoactive nutrients that can improve cerebral perfusion may help to improve a variety of mental disorders.

In presenting our hypothesis, we provide an overview of cerebral vascular function, focusing specifically on the role of the endothelium in CBF and BBB integrity, and review evidence for associations between impaired CBF/endothelial function and psychiatric illness. Then, as an example of a potential treatment, we review the influence of n-3 PUFA on endothelial function, drawing on evidence of anti-inflammatory, anti-aggregatory and vasodilatory roles in blood flow and vascular permeability. We hypothesise that n-3 PUFA may act on the blood side of the BBB as well as on central neural pathways to influence cerebral functions. In the former case, they may act on endothelial cells to influence both vasodilation and selective permeability, thereby assisting in CBF and delivery of oxygen and glucose to brain tissue in response to requirements.

We are now conducting clinical trials to test this hypothesis,
viz. OmegaBrain trial - pilot study with DHA-rich fish oil *(EPAX)*
FOCUS trial - DHA-rich fish oil +/- Curcumin *(Blackmores)*

OmegaBrain Study

Aim: to investigate effects of LCn-3PUFA supplementation for 20 weeks on cerebral circulatory function (assessed by CVR to hypercapnia and cognitive stimuli), mood and cognitive performance in borderline hypertensive adults.

Primary outcome: effect of LCn-3PUFA supplementation on CVR to hypercapnia.

Secondary outcomes: effects of LCn-3PUFA supplementation on

- Cardiovascular parameters, incl. blood pressure and arterial compliance
- CVR to a battery of neuropsychological tests (attention, executive function, working memory, reaction time, dual tasking)
- Neuropsychological test performance
- Erythrocyte fatty acid profiles (Omega-3 Index)

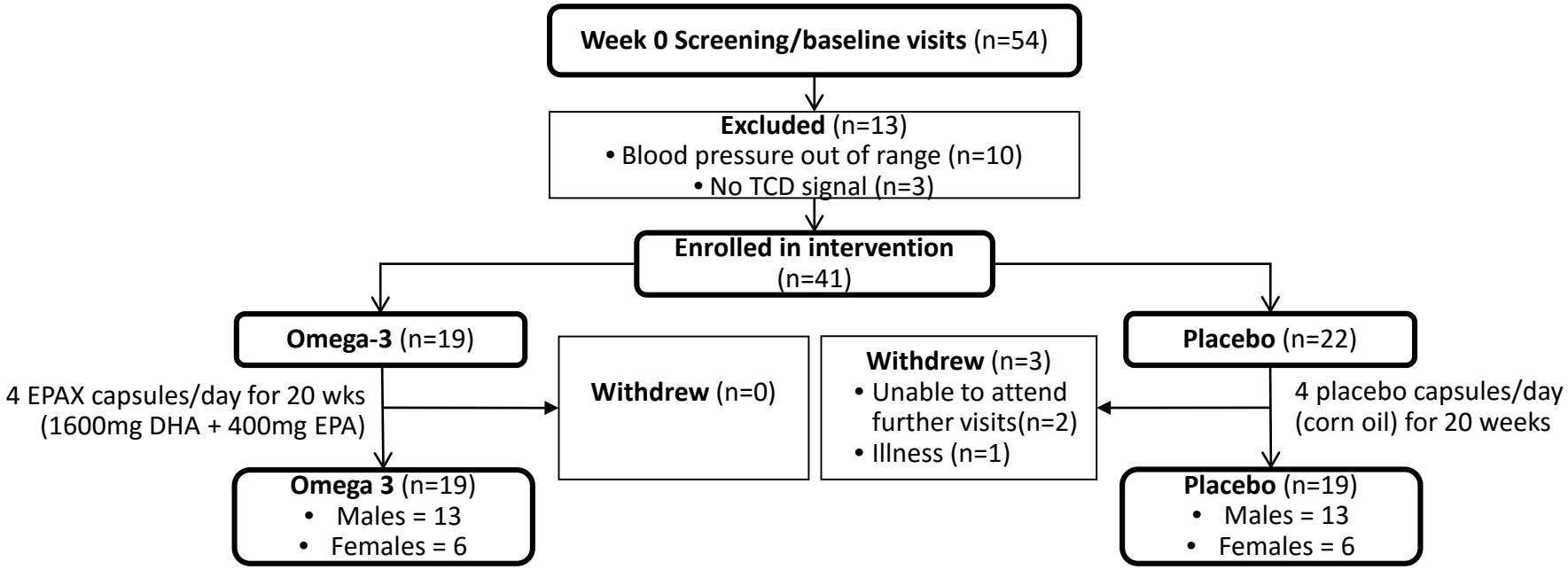
Inclusion criteria

- Aged 40-85 years
- SBP 130-160mmHg or DBP 85-100mmHg
- Consuming <2 fish/seafood meals/week
- Consuming ≤300mg/day of LCn-3PUFA from fish oil or enriched foods
- Unlikely to change medication/supplements during the intervention

Exclusion criteria

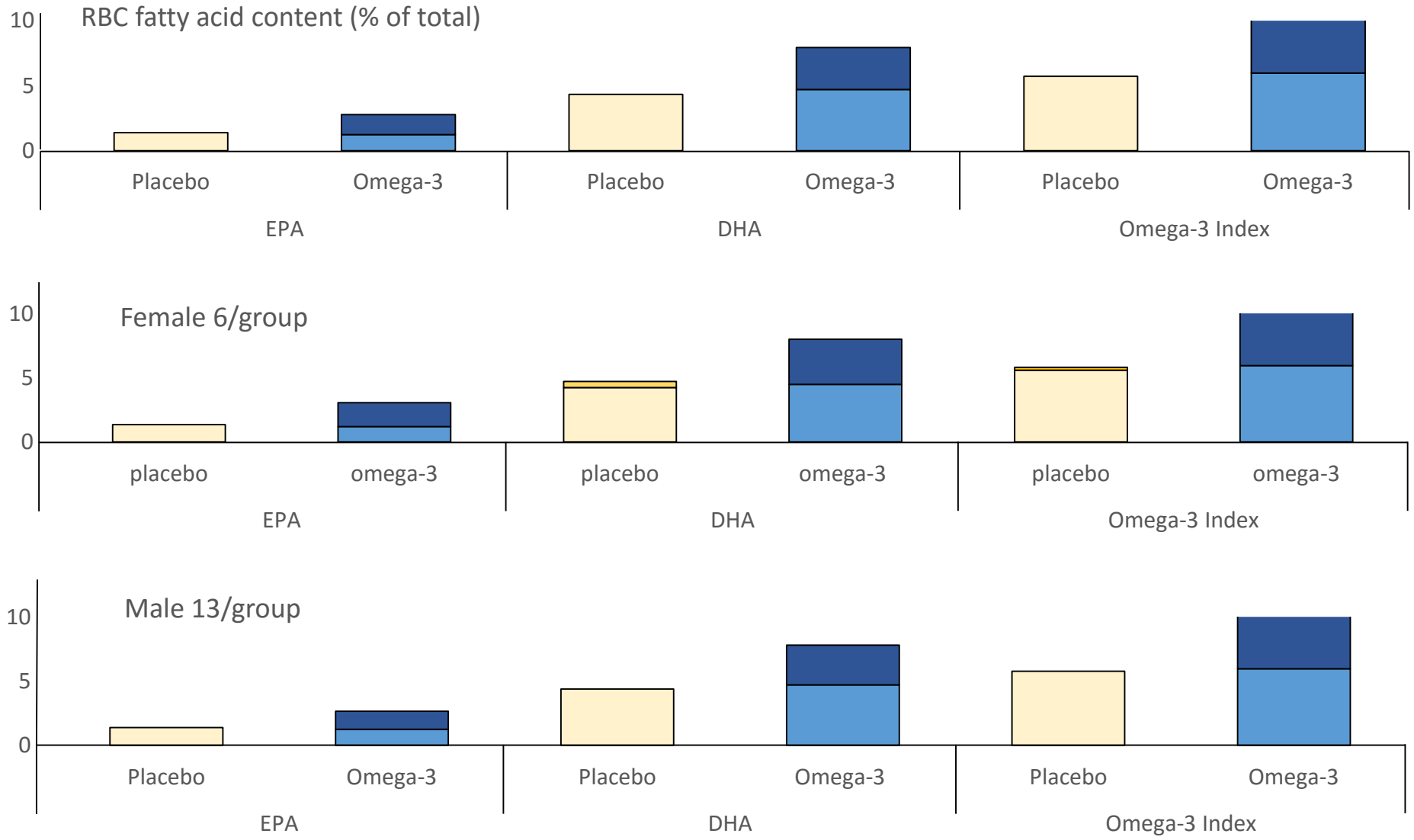
- Suspected dementia (3MS score of < 78/100)
- Smokers or currently on nicotine therapy
- Neurological conditions, heart/kidney/liver disease, diabetes
- Major depression Visual problems
- No measurable TCD signal in MCA

OmegaBrain Study



Baseline characteristics	Placebo	LCn-3PUFA
Age (years)	64.1 ± 2.3	63.2 ± 1.6
Years of formal education	14.7 ± 1.2	16.1 ± 1.1
3MS score (%)	96.3 ± 0.7	96.8 ± 0.7
BMI (kg/m2)	28.8 ± 0.9	26.4 ± 0.8
Waist circumference (cm)	97.9 ± 2.2	93.5 ± 2.9
Clinic systolic BP (mmHg)	141.2 ± 2.0	140.4 ± 1.7
Clinic diastolic BP (mmHg)	79.7 ± 1.7	79.4 ± 1.7
Large artery elasticity (mL/mmHg x 10)	11.4 ± 0.6	12.7 ± 1.0
Small artery elasticity (ml/mmHg x 100)	3.3 ± 0.3	3.3 ± 0.4
Systemic vascular resistance (dyne·sec·cm^{-5})	1758 ± 56	1755 ± 48

OmegaBrain Study



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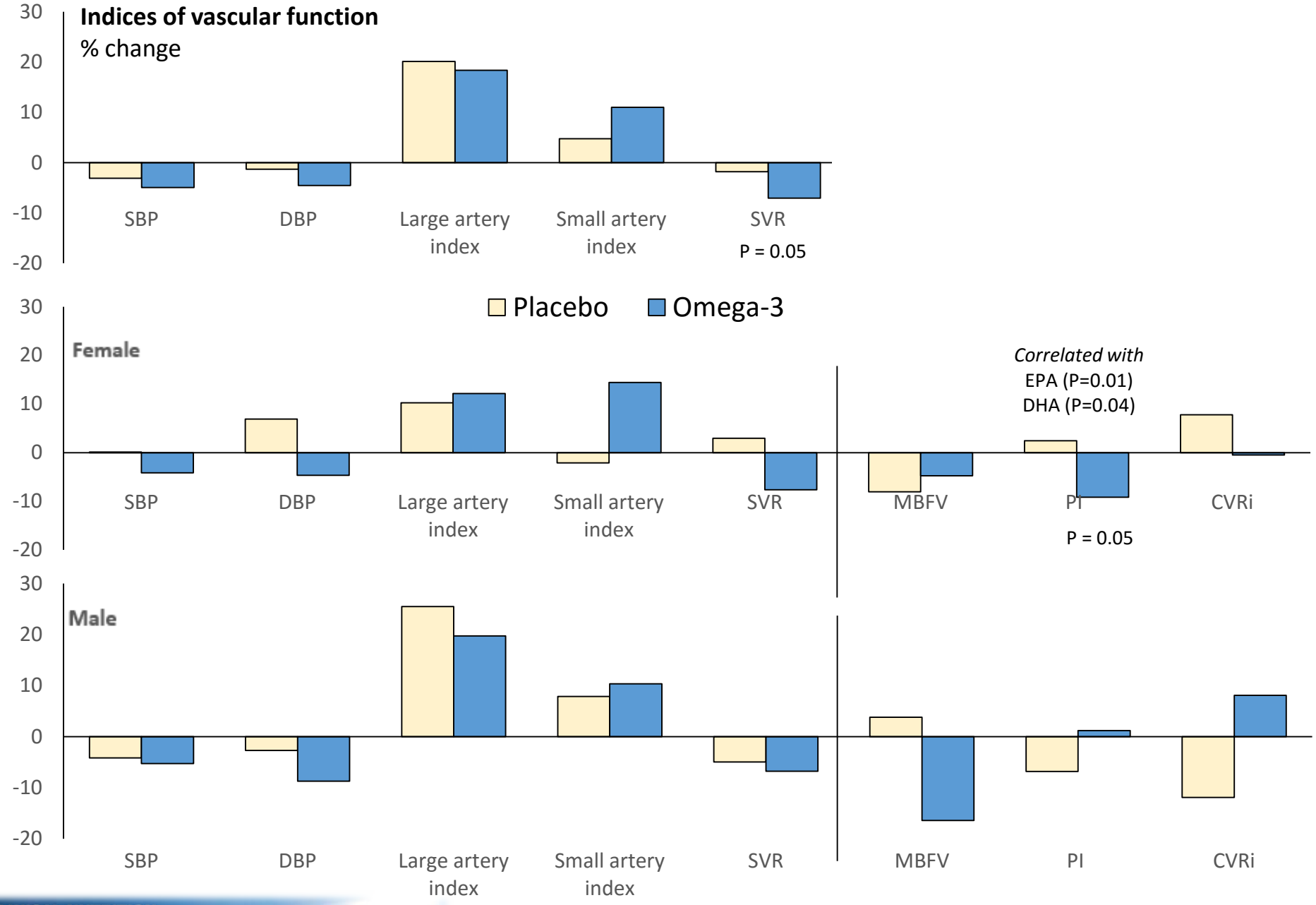

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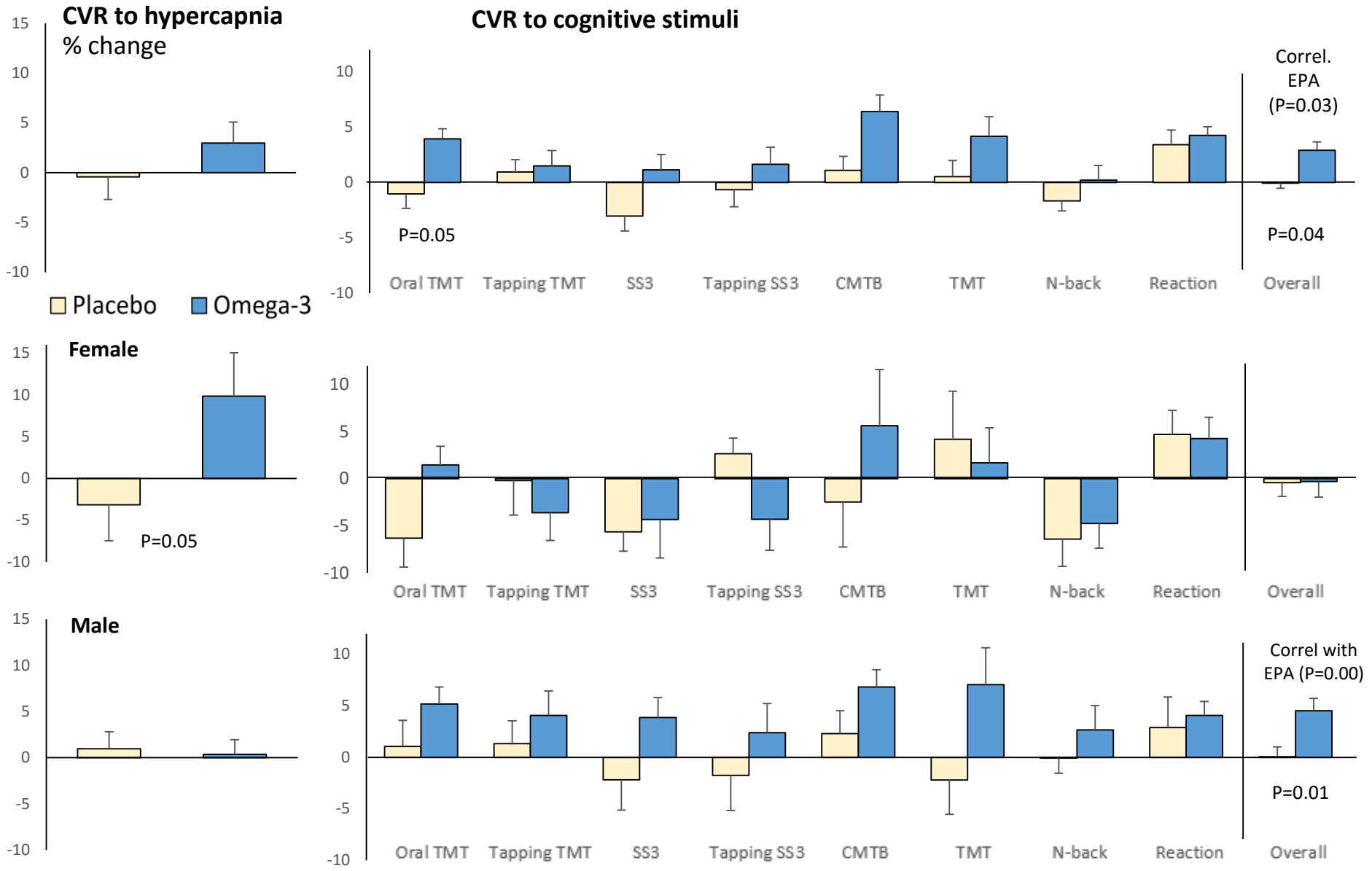

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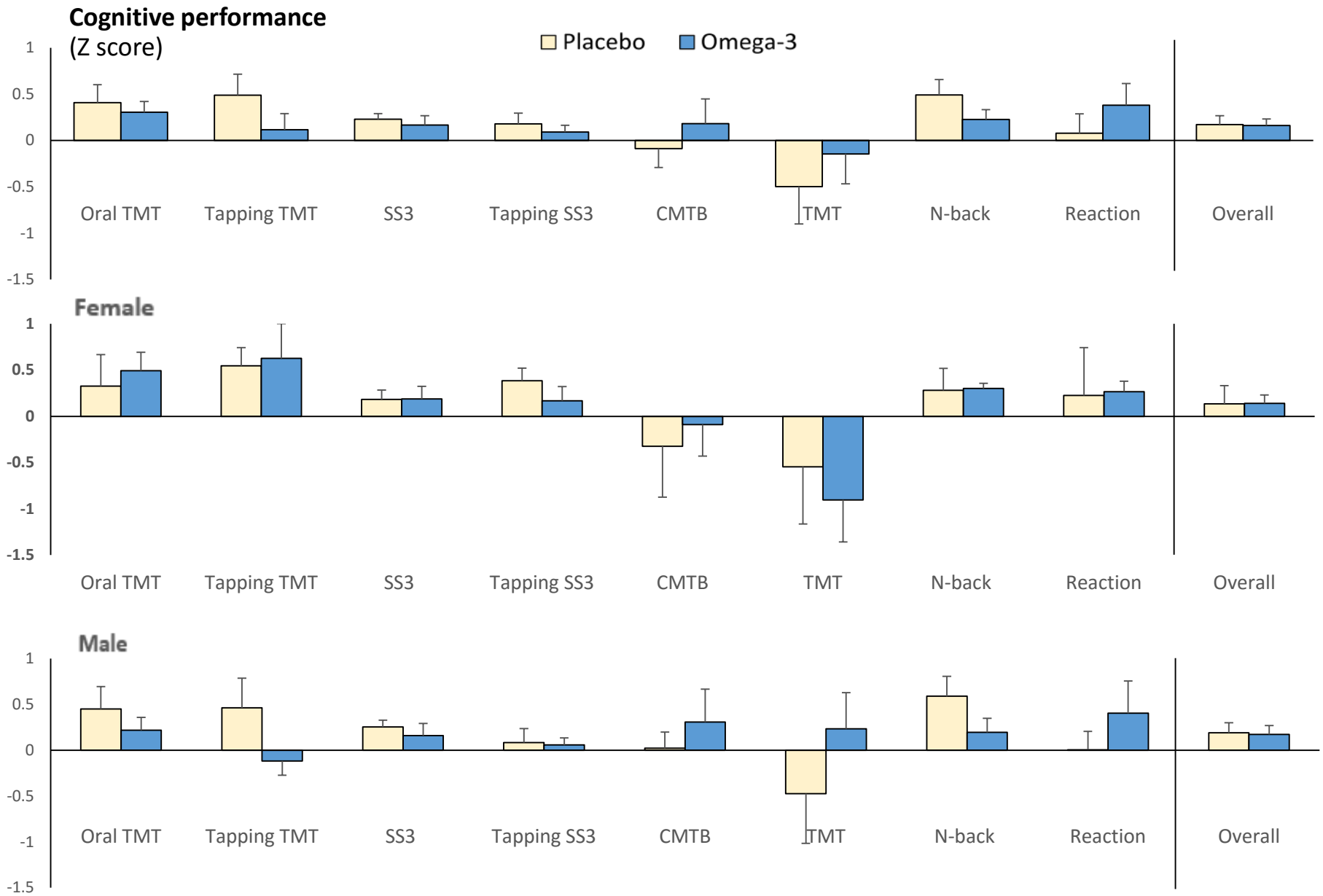

Summary

- Supplementing mildly hypertensive older adults with LCn-3PUFA (1600mg DHA, 400mg EPA) for 20 weeks resulted in modest improvements of cardiovascular and cerebrovascular function.
- CVR to hypercapnia (the primary outcome) tended to increase. This was attributable to a significant 26% increase in women; there was no change in men.
- In contrast, the overall CVR to the cognitive test battery increased significantly; this was due to a significant response in men only, which correlated with the increase of EPA in erythrocytes.
- There was no associated improvement of mood or cognition in either men or women.
- These observations indicate that LCn-3PUFA supplementation has the potential to enhance blood flow in the brain in response to both hypercapnic and cognitive stimuli. Whether this can result in improvements of cognitive performance should be tested in a cognitively impaired population.
- Future studies should examine the differential effects of EPA and DHA and take account of gender differences in responsiveness to supplementation.