Fish oil supplementation increases cerebrovascular responsiveness in women

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Preventive Health for an Aging Population

Functional capacity (physical & mental fitness)

- **Early Life**: Growth and development
- **Adult Life**: Attaining highest level of function
- **Older Age**: Maintaining health and independence

Disability threshold

Range of function in individuals

- genes
- diet
- lifestyle

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 ($\text{TG} \downarrow, \text{HDL} \uparrow$)
- blood pressure
- arterial compliance
- endothelial dilatation
- platelet aggregation
- heart rate
- heart rate variability
- arrhythmia, sudden death
- ischemic heart disease
- heart failure
- kidney damage
- stroke

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**

**Obesity**

**Inflammation**

- high blood pressure
- high blood fats
- high blood glucose, insulin

**↓ mental fitness**

Predisposes to heart disease, diabetes, chronic inflammatory disorders

**Prevalence of obesity in older Australians**

<table>
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<tr>
<th>Year</th>
<th>65+</th>
<th>55–64</th>
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<td>1980</td>
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**Prevalence of self-reported mental disorders**

- 1995
- 2001
- 2004–05

**% Prevalence of diabetes in Australia**

**Prevalence of self-reported mental disorders**

AIHW, 2005

AIHW, 2008

http://www.aihw.gov.au

Dementia is now Australia’s 2nd largest cause of death (ABS, 2016)
Metabolic syndrome is a circulatory disorder

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

**Extracellular matrix factors**
- Fibronectin, laminin
- collagen I, II, III, IV, VIII, XVIII
- proteoglycans

**Anti- and pro-coagulation factors**
- PG\(_I\)\(_2\)
- thrombomodulin
- AT III
- heparin sulfate
- vWF
- TXA\(_2\)
- thromboplastin
- Factor V
- PAF
- PAI-1, PAI-2

**Inflammatory Chemokines and Cytokines**
- IL-1, IL-6, IL-8
- LTB\(_4\), C\(_4\), D\(_4\), E\(_4\)
- MCP-1, MCP-2
- MHC II

**Proteases**
- Thrombin
- MMPs
- tPA

**Growth factors**
- PDGF
- EDGF
- FGF
- IGF
- TGF-β
- GM-CSF
- G-CSF

**Vasorelaxation factors**
- NO
- PG\(_I\)\(_2\)/E\(_2\)
- EDHF

**Vasoconstriction factors**
- TXA\(_2\)/F\(_2\)\(_a\)
- EDCF
- Endothelin
- Leukotrienes
- free radicals

**Flow mediated dilatation (FMD)**
Negative impact of diet/lifestyle on the circulation

- Healthy endothelium:
  - Regulates vasomotor tone
  - Inhibits cell adhesion, platelet aggregation
  - Capillary functions (selective permeability)
  - Integrity of vessel wall (counteracts hypertrophy)

- Arterial disease:
  - Cognitive decline
  - Depression
  - Neurodegenerative disorders
  - Hypertension
  - Coronary disease
  - Heart failure
  - Stroke
  - Renal disease
  - Tissue inflammation
  - Insulin resistance
  - Impaired fat, glucose metabolism
  - Physical incapacity

- 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)

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

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
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)**

*Mean blood flow velocity in the MCA (cm/s)*

**Regional vasodilatation during performance of a cognitive task**

*Mean blood flow velocity in the MCA (cm/s)*

*CVR is maximum increase in blood flow velocity, expressed as % of baseline*
Positive impact of diet/lifestyle on the circulation

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

- arterial disease

- cognitive decline depression
- neurodegenerative disorders
- hypertension coronary disease heart failure strokerenal disease
- tissue inflammation
- insulin resistance
- impaired fat, glucose metabolism
- physical incapacity

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

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

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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
Baseline characteristics

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

RBC fatty acid content (% of total)

Placebo Omega-3 Placebo Omega-3 Placebo Omega-3

EPA          DHA       Omega-3 Index

Female 6/group

placebo  omega-3  placebo  omega-3  placebo  omega-3

EPA          DHA       Omega-3 Index

Male 13/group

Placebo  Omega-3  Placebo  Omega-3  Placebo  Omega-3

EPA          DHA       Omega-3 Index

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Indices of vascular function

% change

OmegaBrain Study

SBP  DBP  Large artery index  Small artery index  SVR

Placebo  Omega-3

Correlated with
EPA (P=0.01)
DHA (P=0.04)

Female

P = 0.05

Male

P = 0.05
OmegaBrain Study

CVR to hypercapnia
% change

CVR to cognitive stimuli

Correl. EPA (P=0.03)
P=0.04

P=0.05

Female

Male

Correl. with EPA (P=0.00)
P=0.01

Placebo  Omega-3

Oral TMT  Tapping TMT  SS3  Tapping SS3  CMTB  TMT  N-back  Reaction  Overall
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.