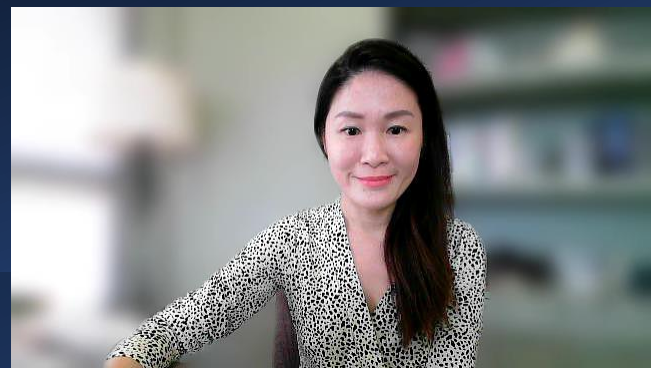
Icosapent Ethyl(EPA) in the treatment of psychiatric disorders

阮綜合醫院身心內科
洪櫻娟醫師
2022/12/04



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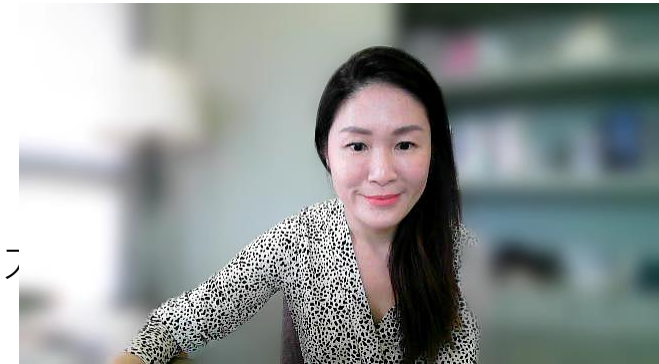
▌專長：

- 情感性疾患，焦慮性疾患
- 婦女身心醫學
- 腫瘤心理醫學
- 舒壓減重門診
- 自律神經失調、慢性疼痛等各種身心壓力



台灣人陷憂鬱症，比你想像更嚴重！

看就醫

問診患者一路升，
去年達63.8萬人

——全台近10年就醫診斷憂鬱症人數

青少年、高齡患者急增

——各年齡層近10年增幅

看用藥

一年1.46億顆抗憂鬱藥下肚

——全台近5年憂鬱症用藥情形

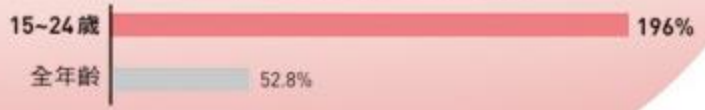
看自我傷害

去年通報自殺4.3萬人，
10年增5成！

——全台近10年通報自殺人數

青少年通報數，更飆近2倍

——青少年與全年齡近10年增幅



註：憂鬱症與自殺高度相關，但並非唯一原因。

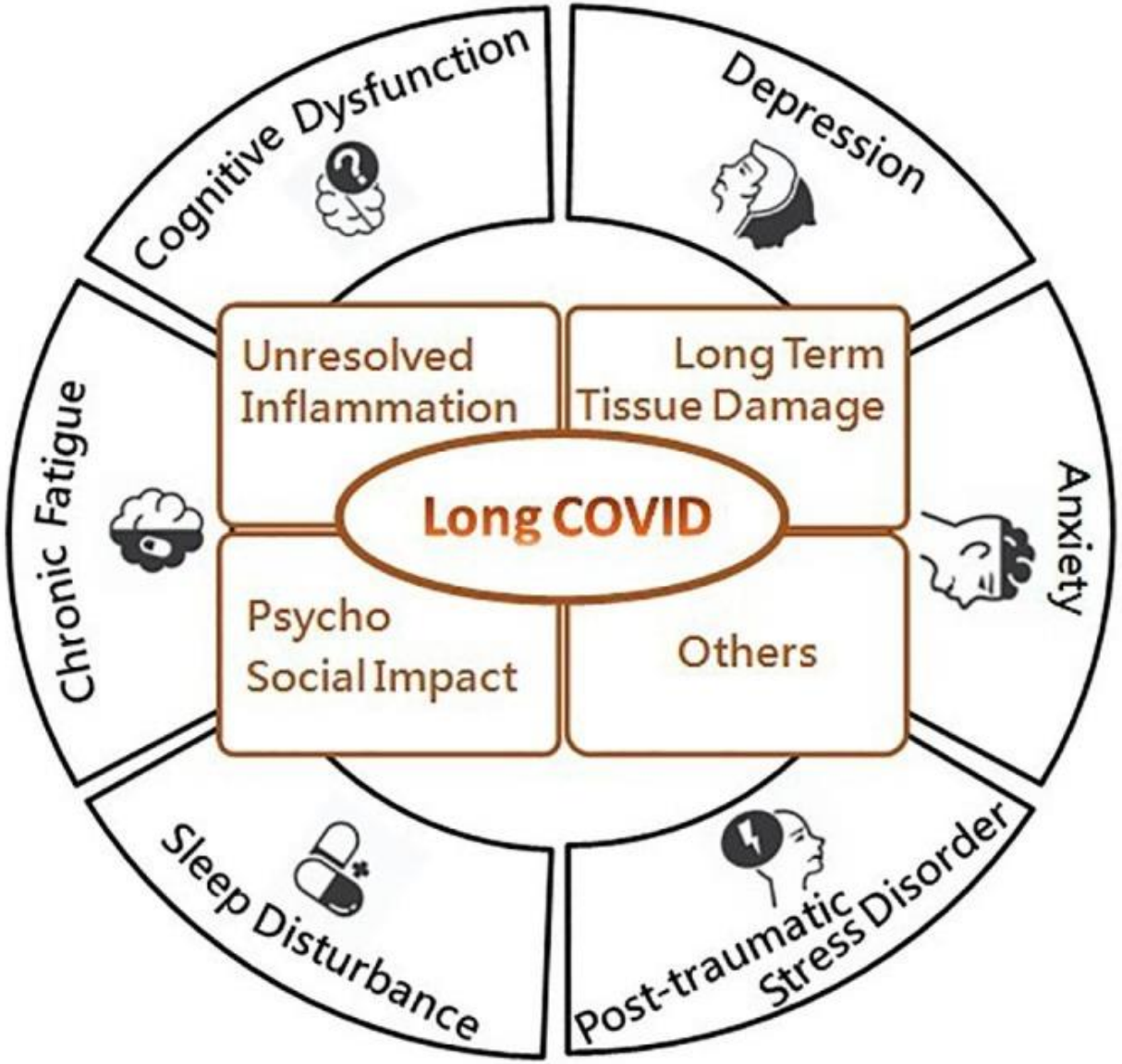
資料來源：健保署、全國自殺防治中心
整理：李浩宇


Brain Fog
After COVID Infection

85% of people with long COVID-19, who weren’t hospitalized, experienced neurological symptoms.

Ann Clin Transl Neurol. 2021 May

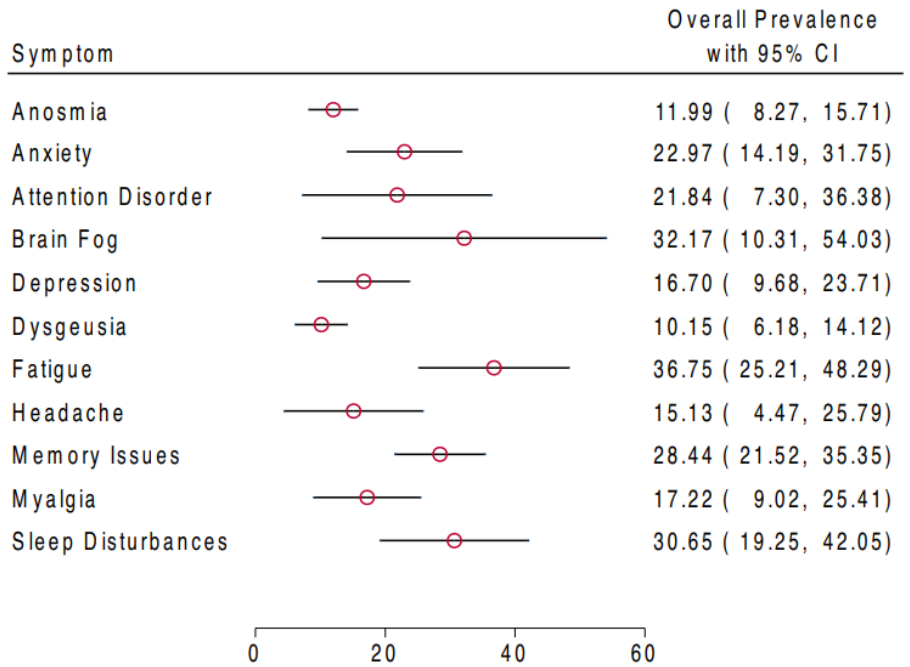
Neuropsychiatric Symptoms of Long COVID

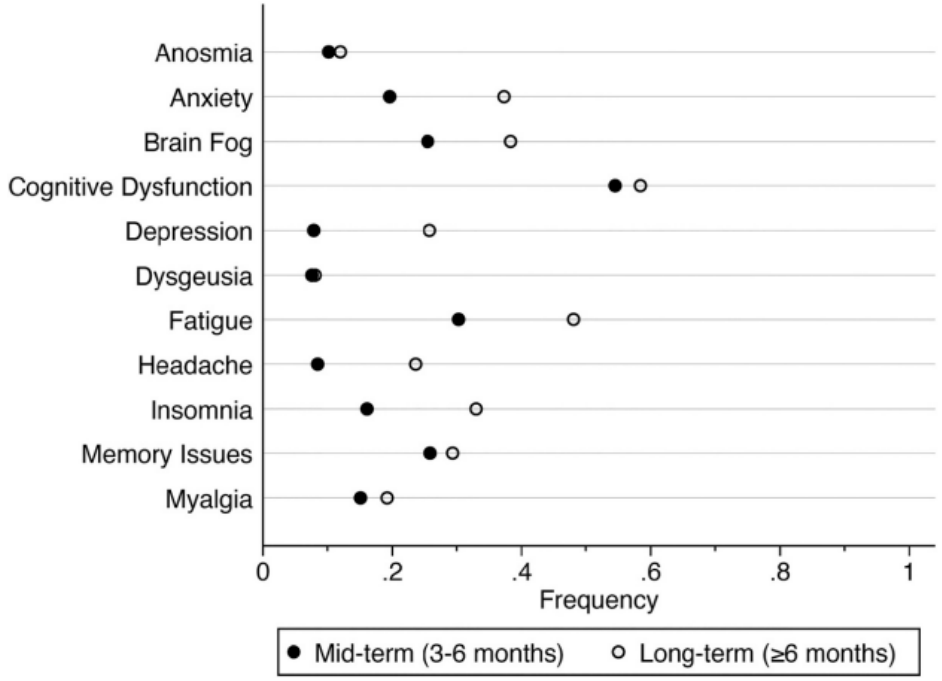


Brain Behav Immun. 2022 Jul

Mid and long-term neurological and neuropsychiatric manifestations of post-COVID-19 syndrome

J Neurol Sci. 2022 Mar





Up to 50% of individuals diagnosed with depression use complementary and alternative medicine (CAM)

BMJ Open. 2019 Aug

GUIDELINES

Management of depression in adults: summary of updated NICE guidance

Tony Kendrick, [1] Steve Pilling, [2,3] Ifigeneia Mavranezouli, [2,3] Odette Megnin-Viggars, [2,3] Catherine Ruane, Hilary Eadon, [4] Navneet Kapur[5,6], on behalf of the Guideline Committee

What you need to know

- Discuss treatment options to match the needs and preferences of a person with a new episode of depression
- Consider the least intrusive and least resource-intensive available treatment (eg, guided self-help) first for less severe depression
- Do not offer antidepressant medication routinely as first line treatment for less severe depression unless that is the person's preference
- When stopping antidepressants, advise a relatively long tapering using a proportional (hyperbolic) reduction schedule

BMJ 2022;378:o1557

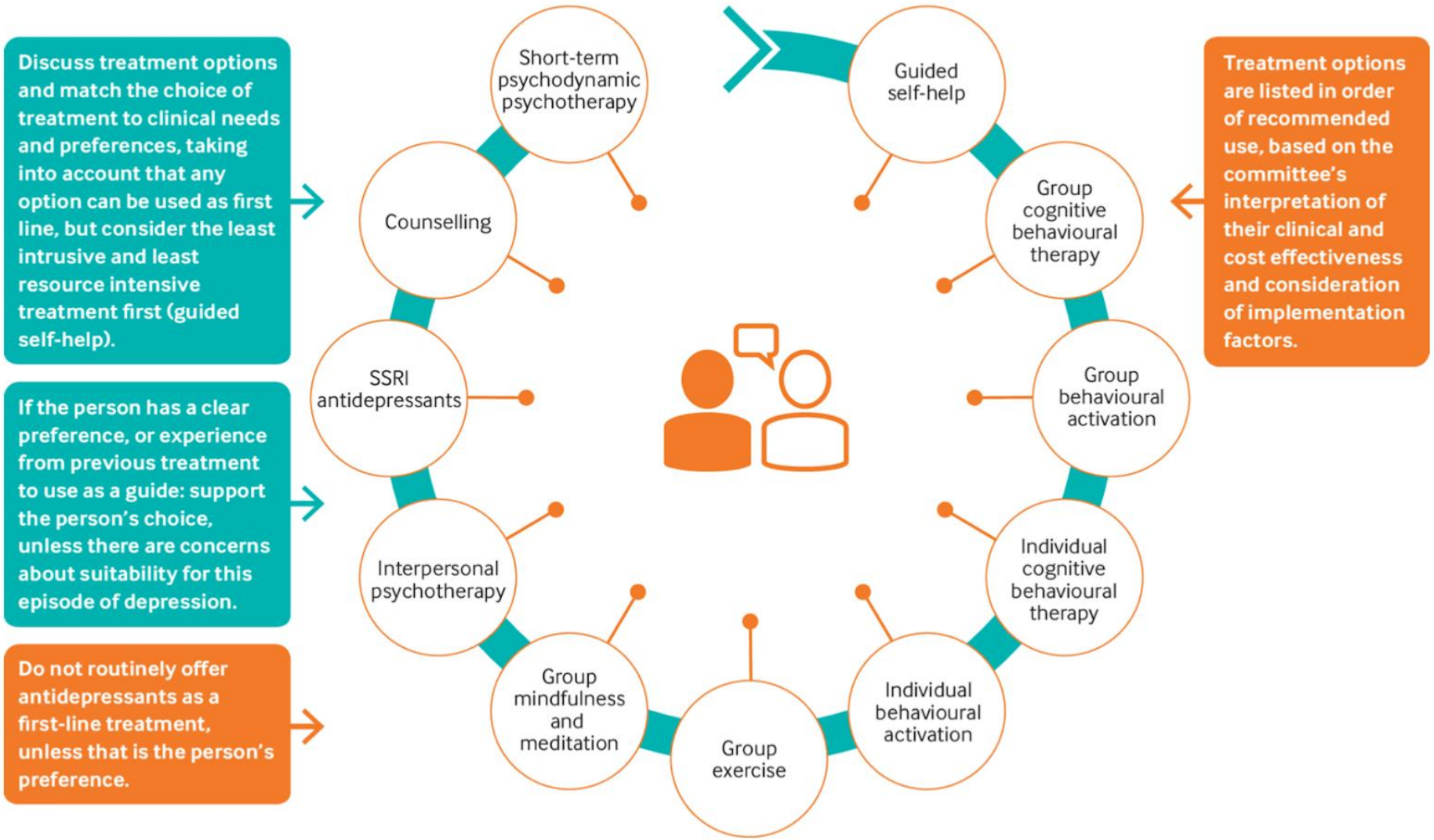


Fig 2 | Visual summary of treatments for less severe depression

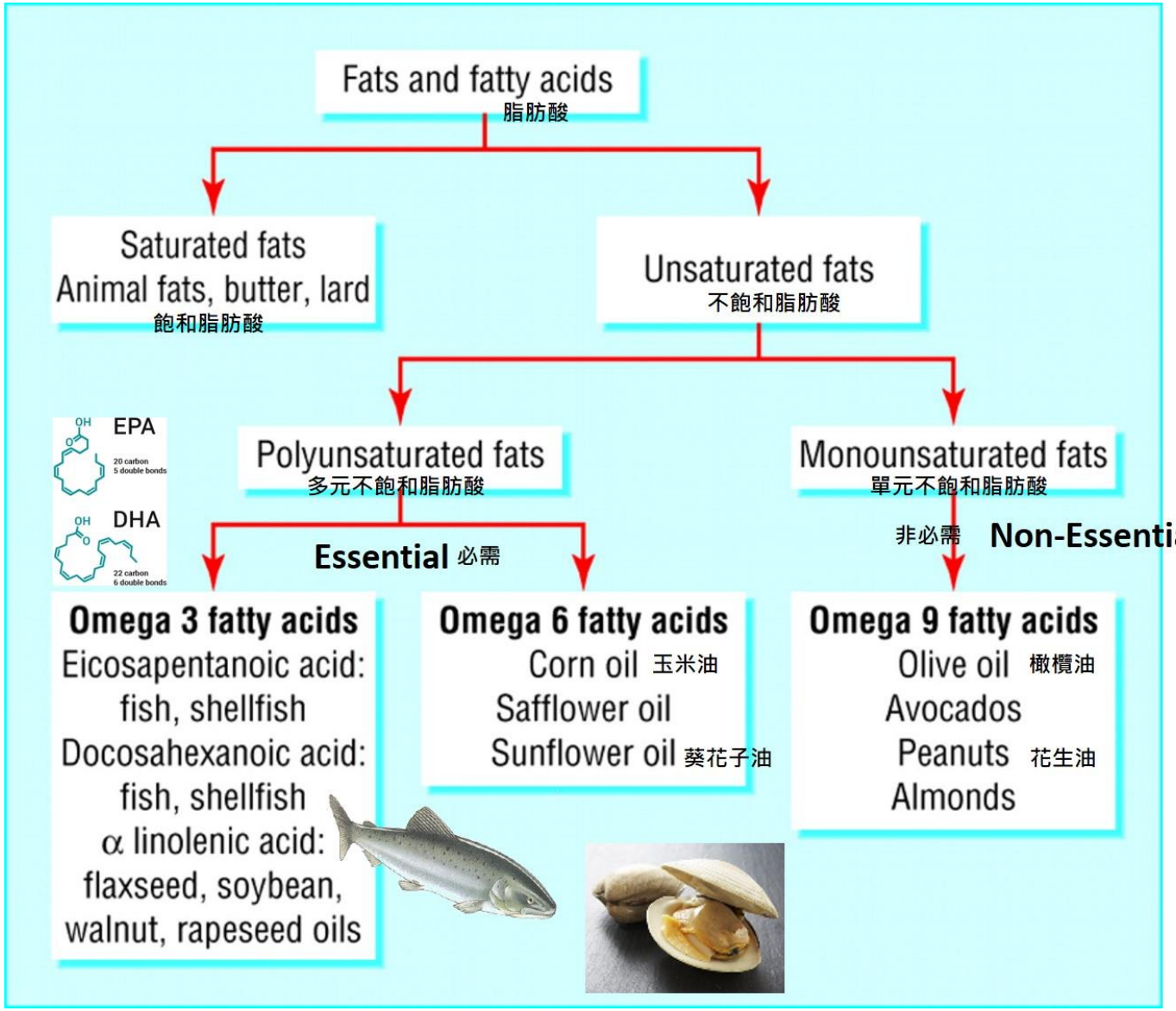
BMJ 2022;378:o1557

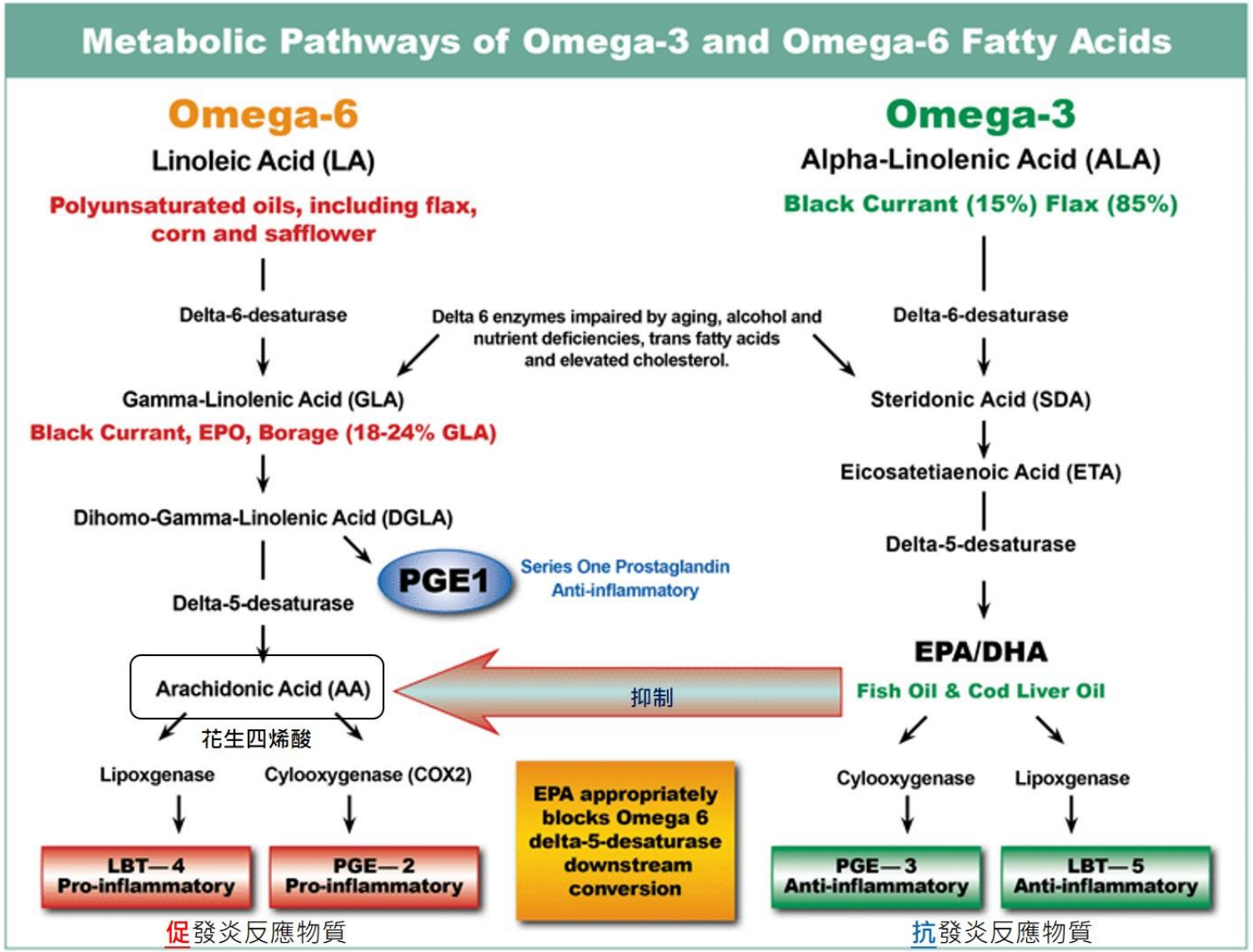
A Model for Shared Decisionmaking

OUTLINE

- Omega-3 in psychopathology across the lifespan
- Omega-3 : Mechanisms of Action
- Omega-3 : Implication in clinical practice

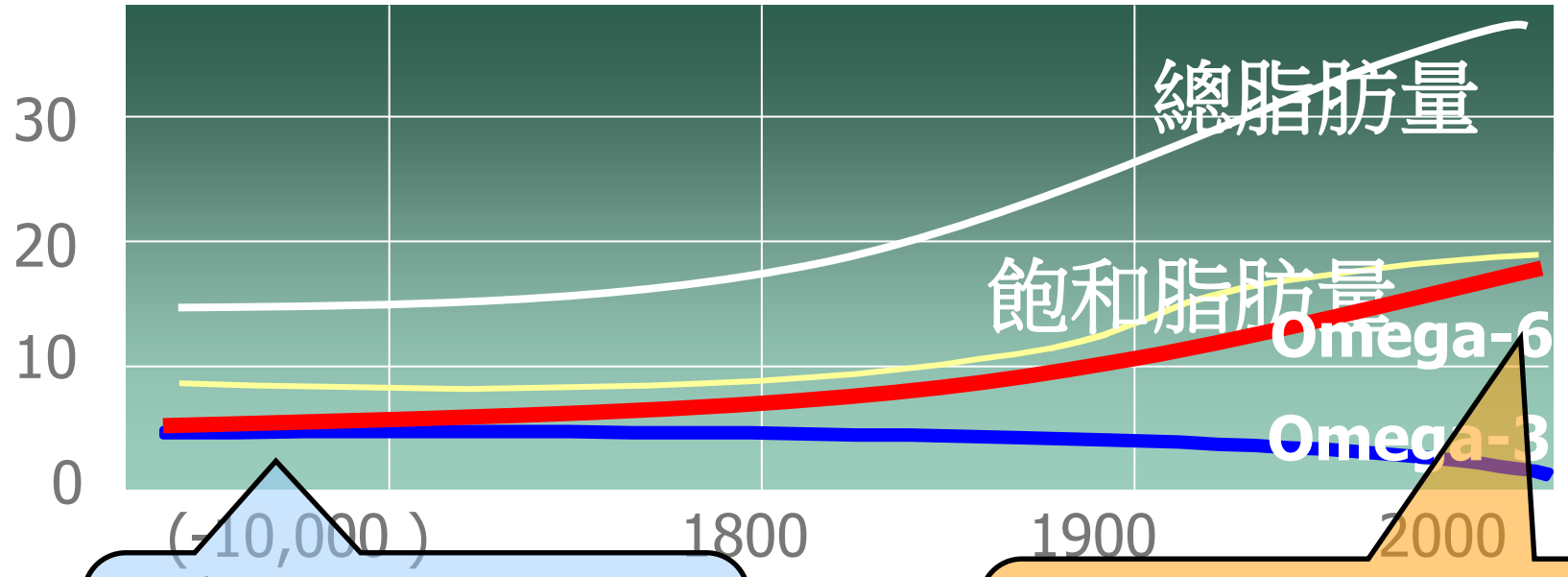
EPA為OMEGA-3家族成員之一




Metabolic Pathways of Omega-3 and Omega-6 Fatty Acids
Omega-6
Linoleic Acid (LA)
Polyunsaturated oils, including flax, corn and safflower
Delta-6-desaturase
Delta 6 enzymes impaired by aging, alcohol and nutrient deficiencies, trans fatty acids and elevated cholesterol.
Gamma-Linolenic Acid (GLA)
Black Currant, EPO, Borage (18-24% GLA)
Dihomo-Gamma-Linolenic Acid (DGLA)
PGE1
Series One Prostaglandin Anti-inflammatory
Delta-5-desaturase
Arachidonic Acid (AA)
抑制
花生四烯酸
Lipoxgenase
Cylooxygenase (COX2)
LBT—4 Pro-inflammatory
PGE—2 Pro-inflammatory
EPA appropriately blocks Omega 6 delta-5-desaturase downstream conversion
促發炎反應物質
Omega-3
Alpha-Linolenic Acid (ALA)
Black Currant (15%) Flax (85%)
Delta-6-desaturase
Steridonic Acid (SDA)
Eicosatetiaenoic Acid (ETA)
Delta-5-desaturase
EPA/DHA
Fish Oil & Cod Liver Oil
Cylooxygenase
Lipoxgenase
PGE—3 Anti-inflammatory
LBT—5 Anti-inflammatory
抗發炎反應物質

OMEGA-3
可抗發炎

人類攝取OMEGA3比例的逐漸失衡



過去
Omega-6 : Omega-3
攝取均衡比率約為1:1

如今
Omega-6 : Omega-3
已偏離將近至20:1

PUFAs comprise 80% of total membrane phospholipids

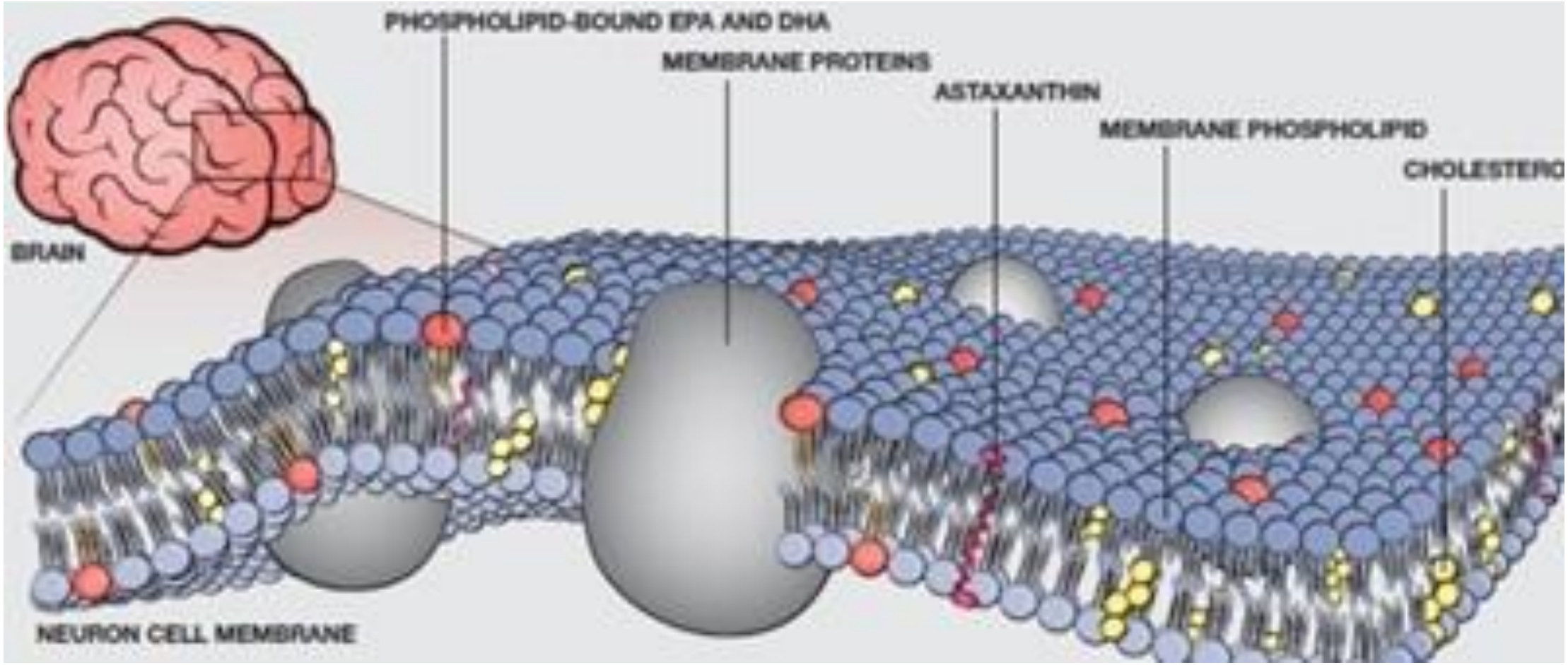
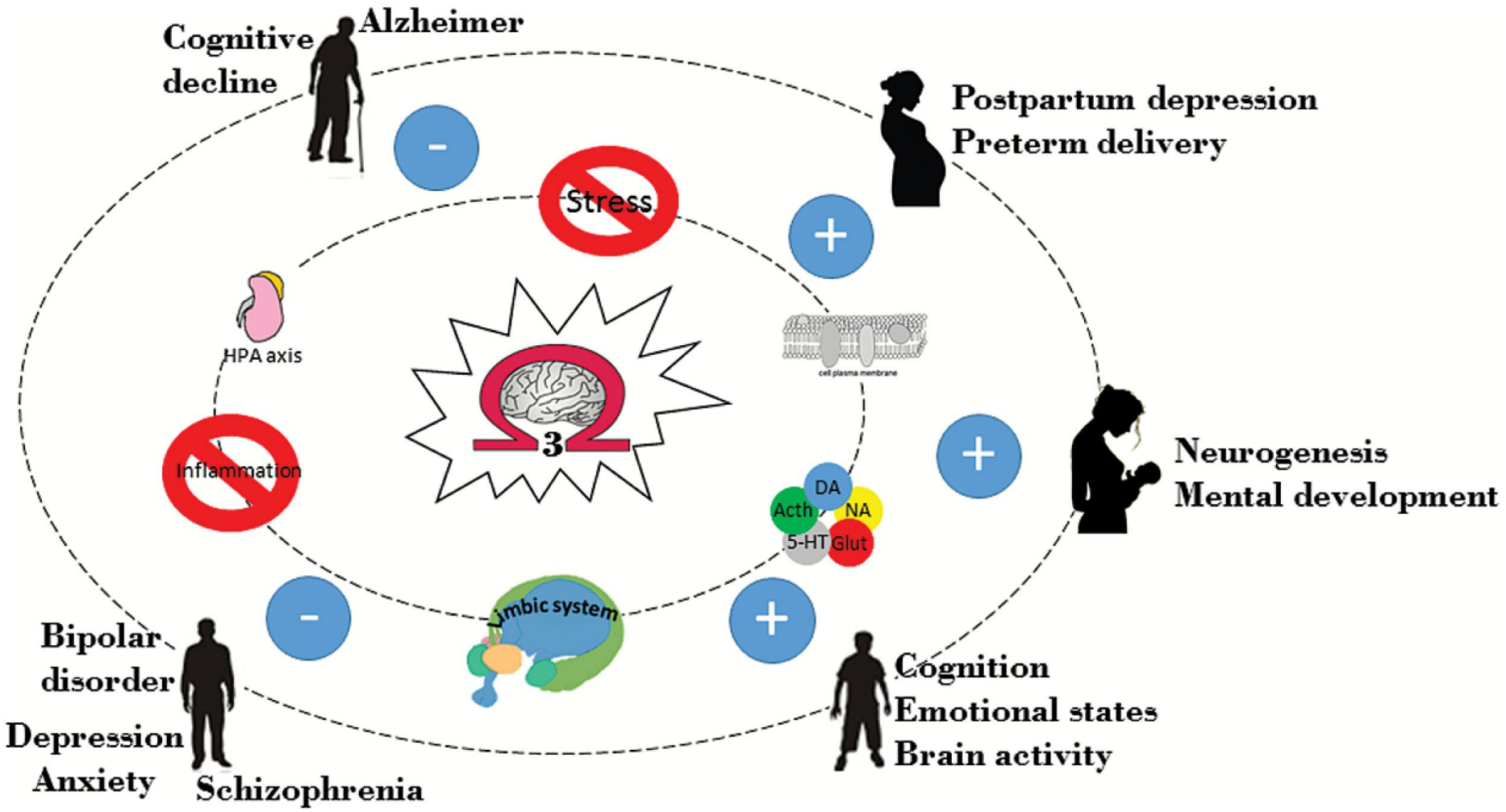
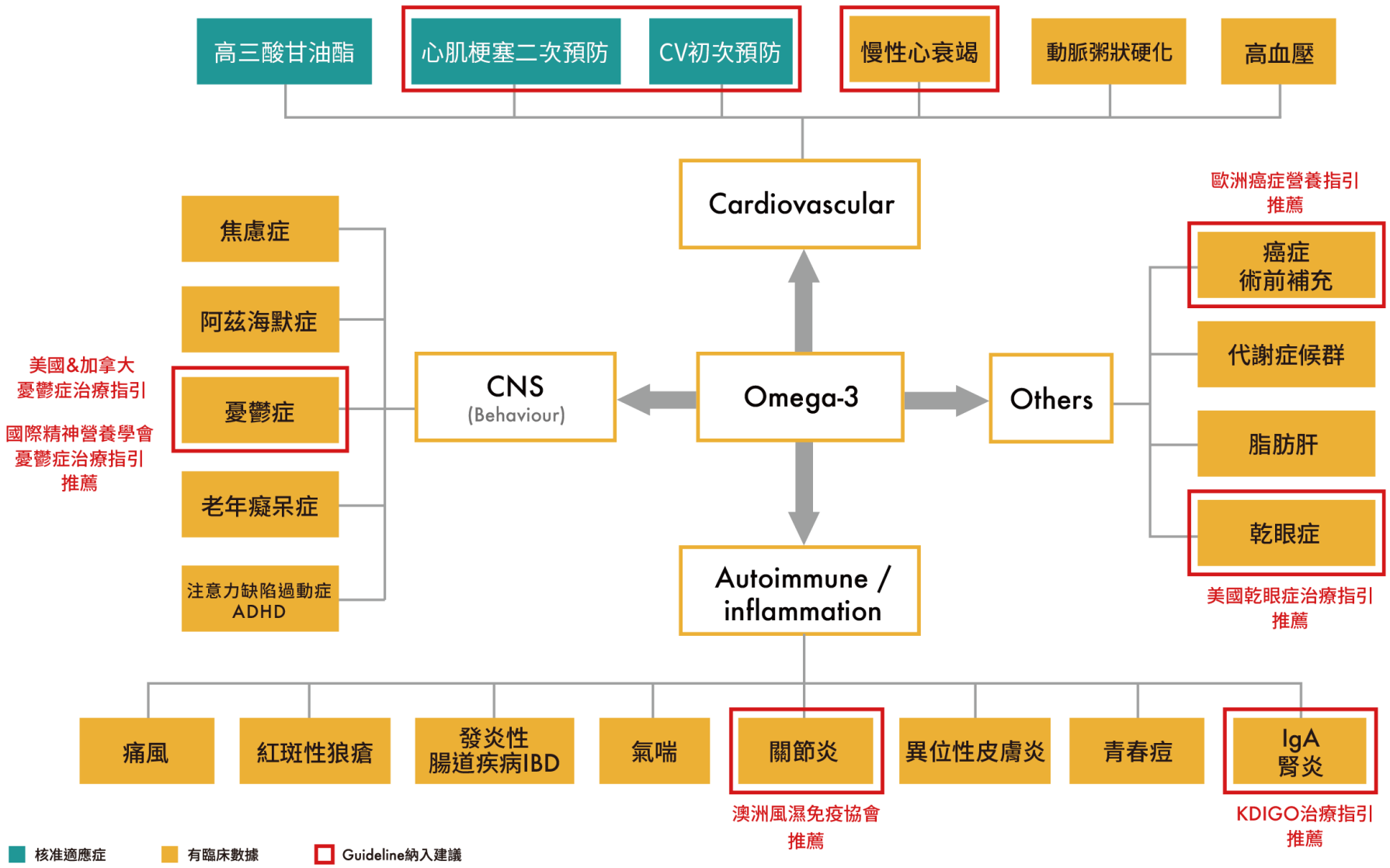


Figure 1. Omega-3 polyunsaturated fatty acids [(n-3) PUFAs] throughout the lifespan.



Int J Neuropsychopharmacol. 2016 Dec 30;19(12):pyw078.

OMEGA-3 臨床實證一覽




A
D
H
D

n-3 PUFAs in Early-Life: From Embryogenesis to Adolescence

- n-3 PUFAs are involved in important phases of brain development such as neurogenesis, myelination, synaptogenesis, and dendritic arborisation. (Wurtman, 2014)
- Benefits of DHA supplementation in brain activity and school performance from over one-half of the considered studies. (Kuratko, 2013)
- Benefits of n-3 PUFAs in learning and cognitive performance, particularly in malnourished subjects. (Dalton et al., 2009) (Portillo-Reyes et al., 2014)

Deficit in n-3 PUFAs: Implication for Childhood Disorders

- Deficits in n-3 PUFAs have been associated with higher risk of development of childhood disorders such as ADHD (Richardson and Ross, 2000).
- Moreover, behavioral and learning problems, such as anomalous visual, motor, attention, and language processing, have been linked to lower n-3 PUFAs plasma levels (Richardson, 2004).

ADHD患者血中Omega3較正常人低

ADHD和正常人Omega6/3血中濃度比較

Figure 2. Blood omega-6 to omega-3 ratio in patients with ADHD vs. control subjects

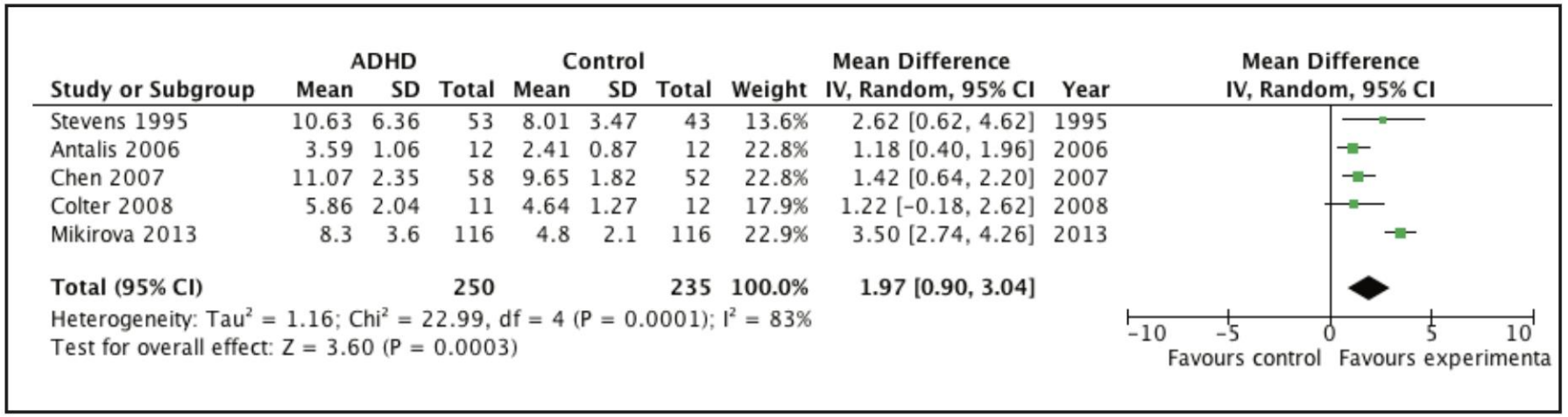
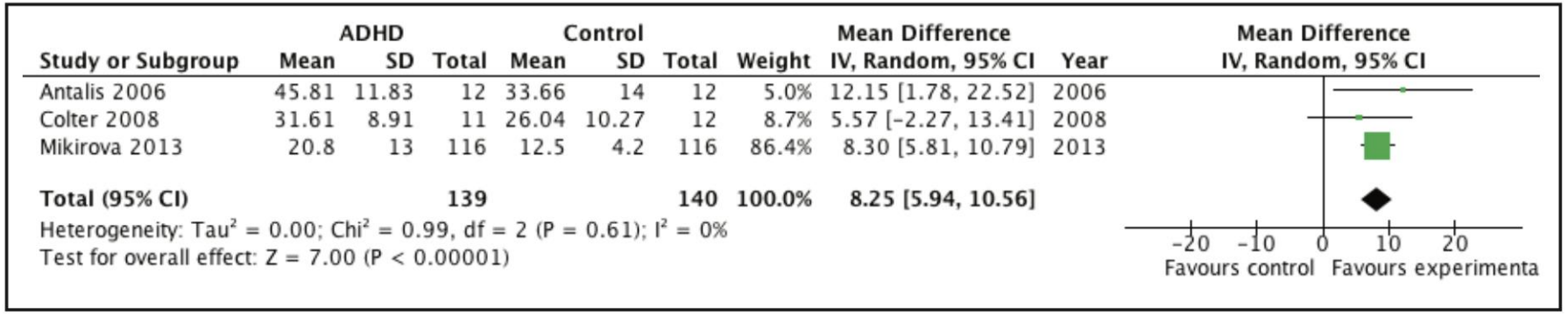


Figure 3. Blood arachidonic acid (AA) to eicosapentaenoic acid (EPA) ratio in patients with ADHD vs. control subjects

ADHD和正常人AA/EPA血中濃度比較



J Can Acad Child Adolesc Psychiatry, 25:2, Spring 2016

Omega -3 fatty acid supplementation demonstrated a small but significant effect in improving ADHD symptoms

Study or Subgroup	Weight	Std. Mean Difference IV, Fixed, 95%CI	Year
Voigt 2001[44]	8.0%	0.04 [-0.49, 0.58]	2001
Richardson 2002[42]	4.1%	0.38 [-0.37, 1.13]	2002
Stevens 2003[25]	4.8%	0.40 [-0.29, 1.09]	2003
Richardson 2005[41]	17.3%	0.36 [-0.00, 0.73]	2005
Sinn 2007[45]	11.6%	0.58 [0.13, 1.02]	2007
Vaisman 2008[43] fishoil	6.3%	0.17 [-0.44, 0.77]	2008
Johnson 2008[39]	11.1%	0.35 [-0.11, 0.81]	2008
Vaisman 2008[43] omega-3	5.7%	0.41 [-0.22, 1.05]	2008
Raz 2009[40]	9.6%	0.13 [-0.36, 0.62]	2009
Gustafsson 2009[46]	13.8%	0.22 [-0.19, 0.62]	2009
Belanger 2010[47]	7.7%	0.40 [-0.15, 0.95]	2010
Total (95% CI)	100.0%	0.31 [0.16, 0.47]	

Heterogeneity: $Chi^2 = 3.68$, $df = 10$ ($P = 0.96$); $I^2 = 0\%$

Test for overall effect: $Z = 4.04$ ($P < 0.0001$)

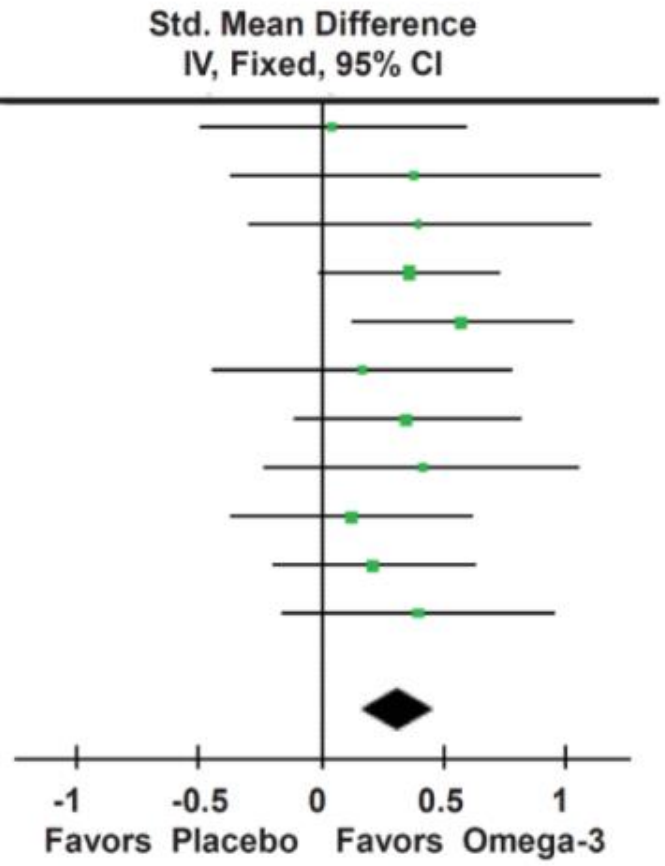
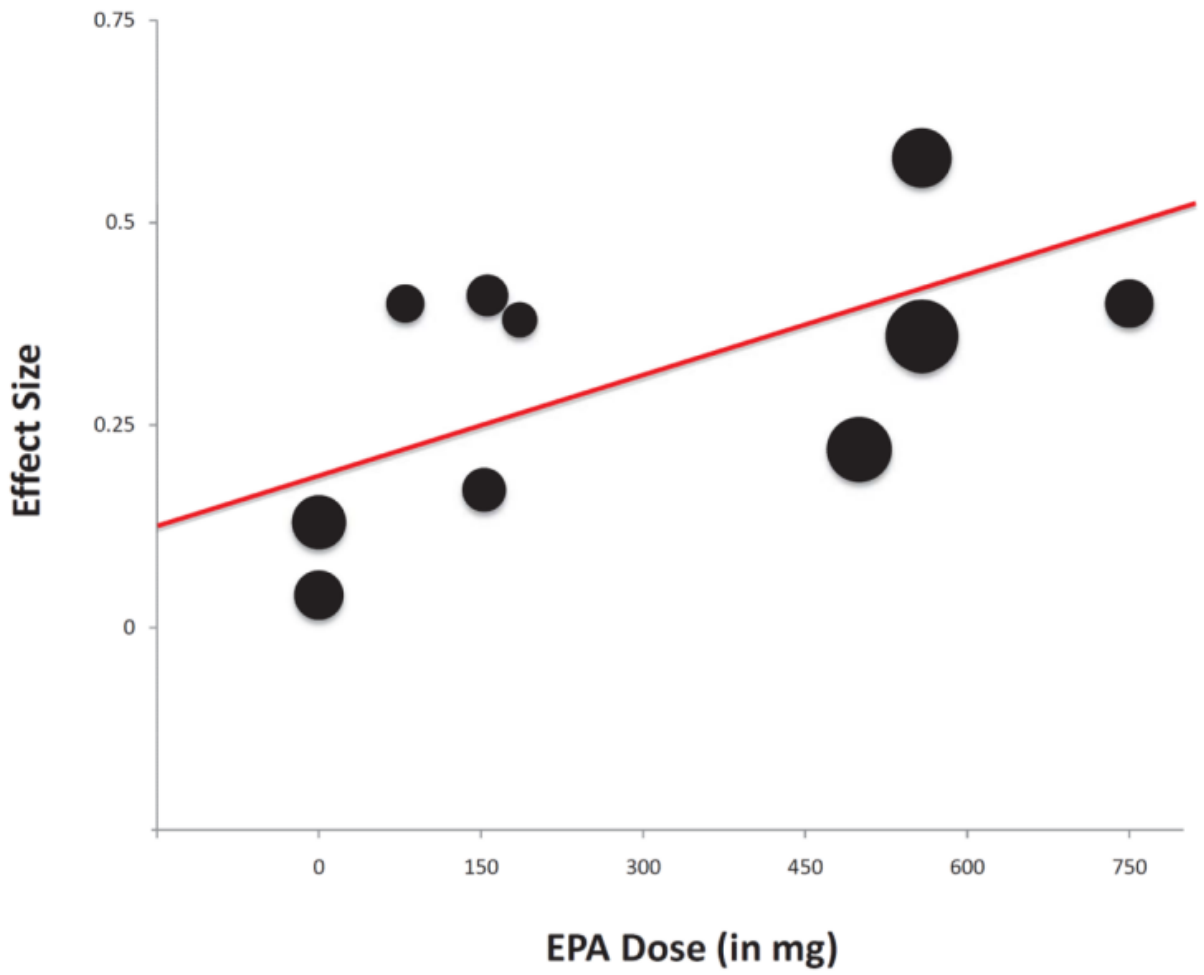


Figure 2. Omega-3 Fatty Acid Supplementation for Attention-Deficit Hyperactivity Disorder (ADHD)

Bloch and Qawasmi, 2011

Figure 3. EPA dose and Efficacy of Omega-3 Fatty Acid Supplementation for ADHD



J Am Acad Child Adolesc Psychiatry. 2011 Oct;50(10):991-1000.

Omega-3 Supplementation in ADHD

Meta-Analysis of 10 trials involving 699 children with ADHD

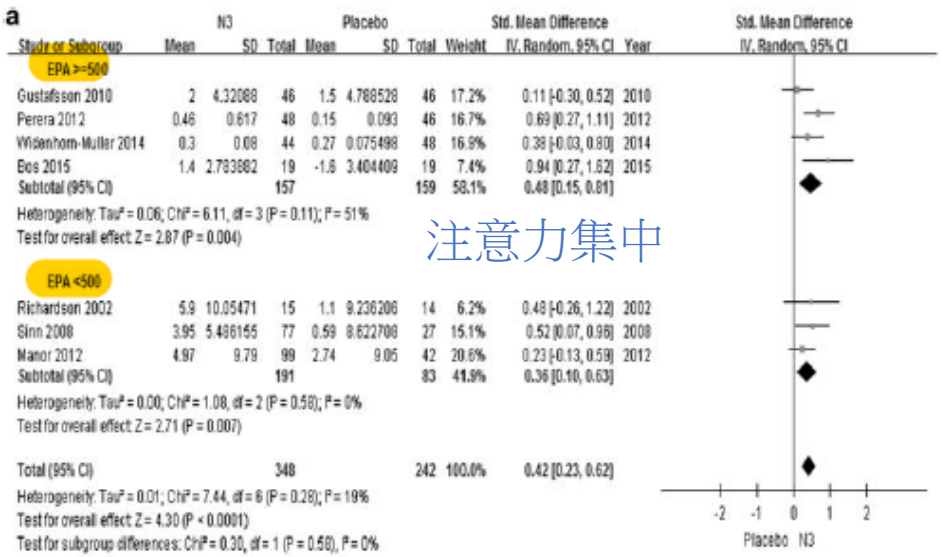
- Higher doses of EPA within essential fatty acids supplements was significantly associated with increased efficacy in treating ADHD symptoms
- It may be reasonable to use omega-3 fatty supplementation to augment traditional pharmacological interventions or for families who decline other psychopharmacological options.

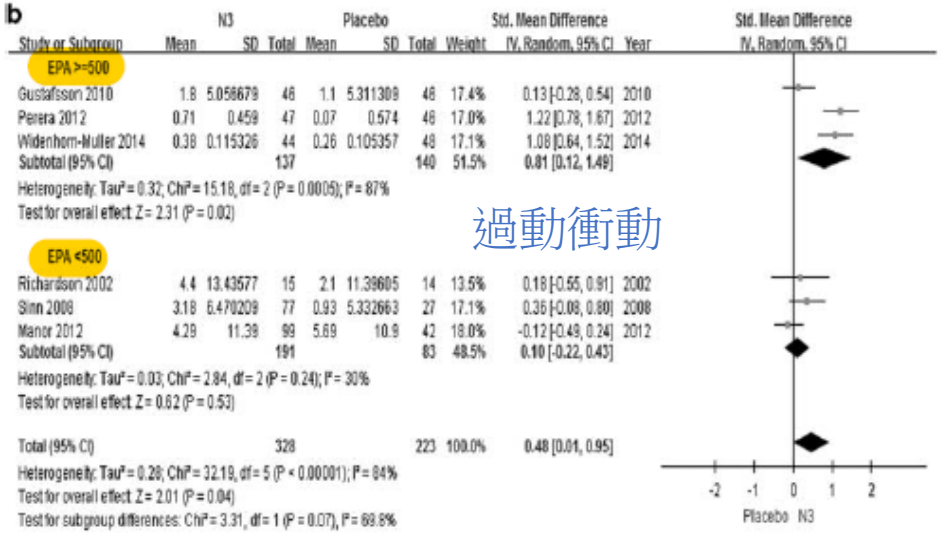
2018年統合分析也顯示，EPA須≥500mg 方能有效改善過動(ADHD)相關症狀

(1)Only studies with EPA dose of > 500 mg improve hyperactivity symptoms.

(2)EPA supplementation dosage >500 mg should be considered when treating youth with ADHD, especially those with predominantly hyperactivity/impulsivity presentation.

Dr Kuan-Pin Su





Neuropsychopharmacology (2018) 43, 534–545

2019臨床研究顯示，給予ADHD患者高劑量純DHA並沒有改善效益 !!!

(1)RCT
(2)N = 66 patients with ADHD, aged between 6 and 18 years
(3)ω-3 fatty acids = **1000mgDHA** + 90mg EPA , follow 6 months

Table 1 Changes of variables of the d2 test at the end of the study as compared with baseline in the two study groups (within-group comparisons)

d2 variables	DHA group (*n*=32)			Placebo group (*n*=34)			Interaction (time x group)
	Baseline mean (SD)	At 6 months mean (SD)	*P*-value (ES)	Baseline mean (SD)	At 6 months mean (SD)	*P*-value (ES)	*P*-value (ES)
TOT	316.1 (91.4)	373.5 (94.9)	< 0.001 (0.534)	330.1 (96.0)	381.8 (11.6)	<0.001 (0.439)	0.694 (0.002)
TR	329.6 (88.7)	382.8 (97.0)	< 0.001 (0.507)	343.6 (93.6)	394.1 (112.7)	< 0.001 (0.408)	0.853 (0.001)
TA	130.9 (37.4)	153.4 (39.3)	< 0.001 (0.508)	132.8 (40.6)	154.6 (52.0)	< 0.001 (0.416)	0.915 (< 0.001)
O	9.2 (12.2)	8.3 (7.9)	0.716 (0.004)	12.3 (13.3)	9.5 (11.8)	0.231 (0.043)	0.566 (0.005)
C	4.8 (6.9)	1.1 (1.3)	0.005 (0.224)	3.1 (5.4)	1.2 (1.6)	0.035 (0.127)	0.258 (0.020)
CON	126.4 (41.4)	152.1 (39.7)	< 0.001 (0.497)	129.6 (43.1)	151.9 (54.9)	< 0.001 (0.427)	0.604 (0.004)
VAR	12.6 (4.2)	13.9 (4.8)	0.291 (0.036)	13.4 (5.1)	13.7 (5.3)	0.831 (0.001)	0.573 (0.005)

Abbreviations: ES, effect size; TOT, total test effectiveness; TR, total number of responses; TA, total number of correct answers; O, omissions; C, commissions; CON, concentration index; VAR, variability.

Neuropsychiatric Disease and Treatment 2019:15

有沒有6歲以前的臨床研究?
6歲以前可不可以使用？是否安全？

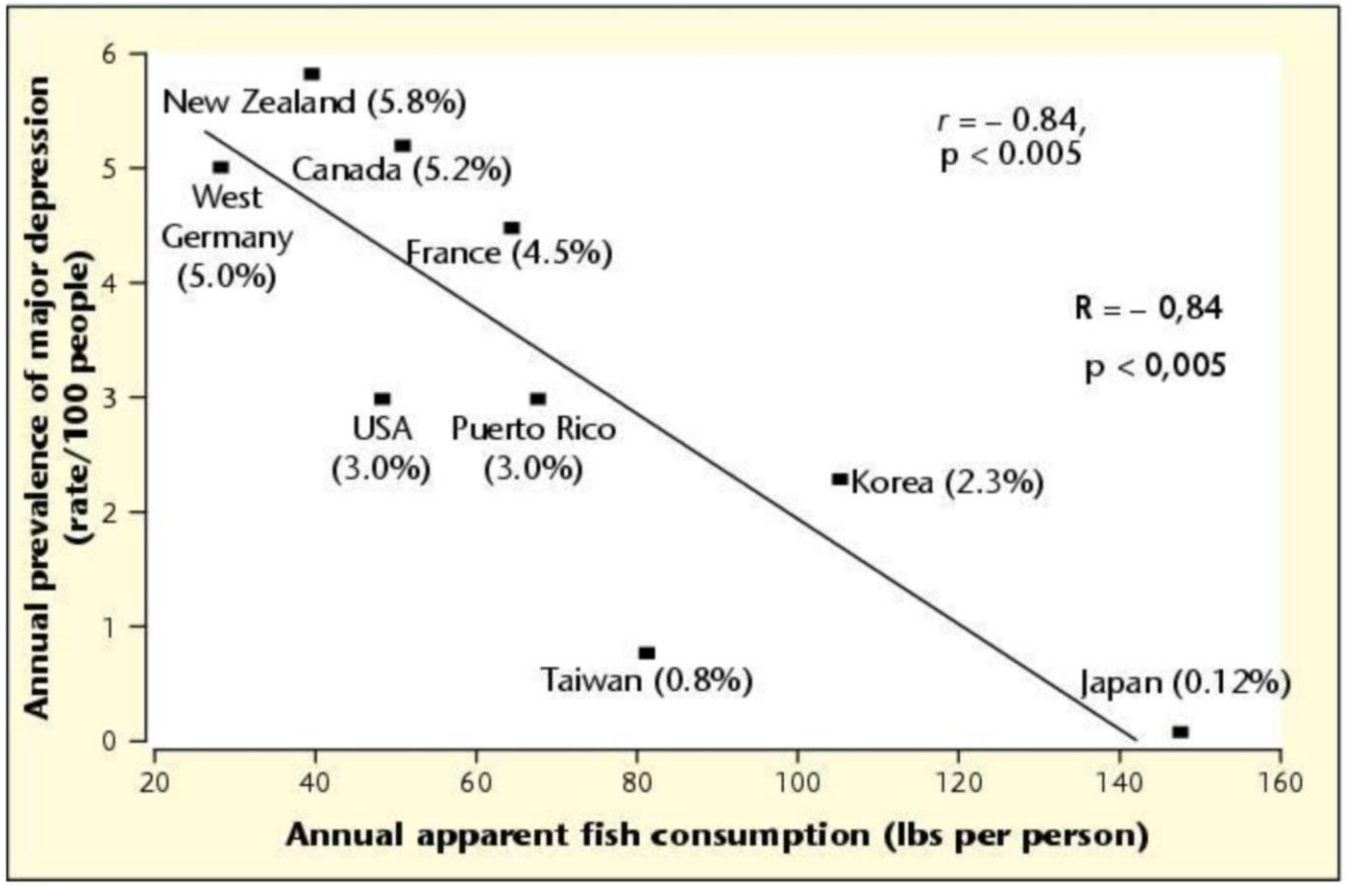
Life Stage	Recommended Amount
Birth to 12 months*	0.5 g
Children 1–3 years	0.7 g
Children 4–8 years	0.9 g
Boys 9–13 years	1.2 g
Girls 9–13 years	1.0 g
Teen boys 14–18 years	1.6 g
Teen girls 14–18 years	1.1 g
Men	1.6 g
Women	1.1 g
Pregnant teens and women	1.4 g
Breastfeeding teens and women	1.3 g

*As total omega-3s. All other values are for ALA alone.

- 目前臨床研究都未包含學齡前
- 6歲以前可以用，劑量建議為EPA 0.5g
- 根據美國國家衛生研究院建議，新生兒即建議補充每日Omega-3(EPA/DHA) 0.5g以上

Major Depressive Disorder

1998年大型觀察性研究發現憂鬱症盛行率與漁獲消耗量有關

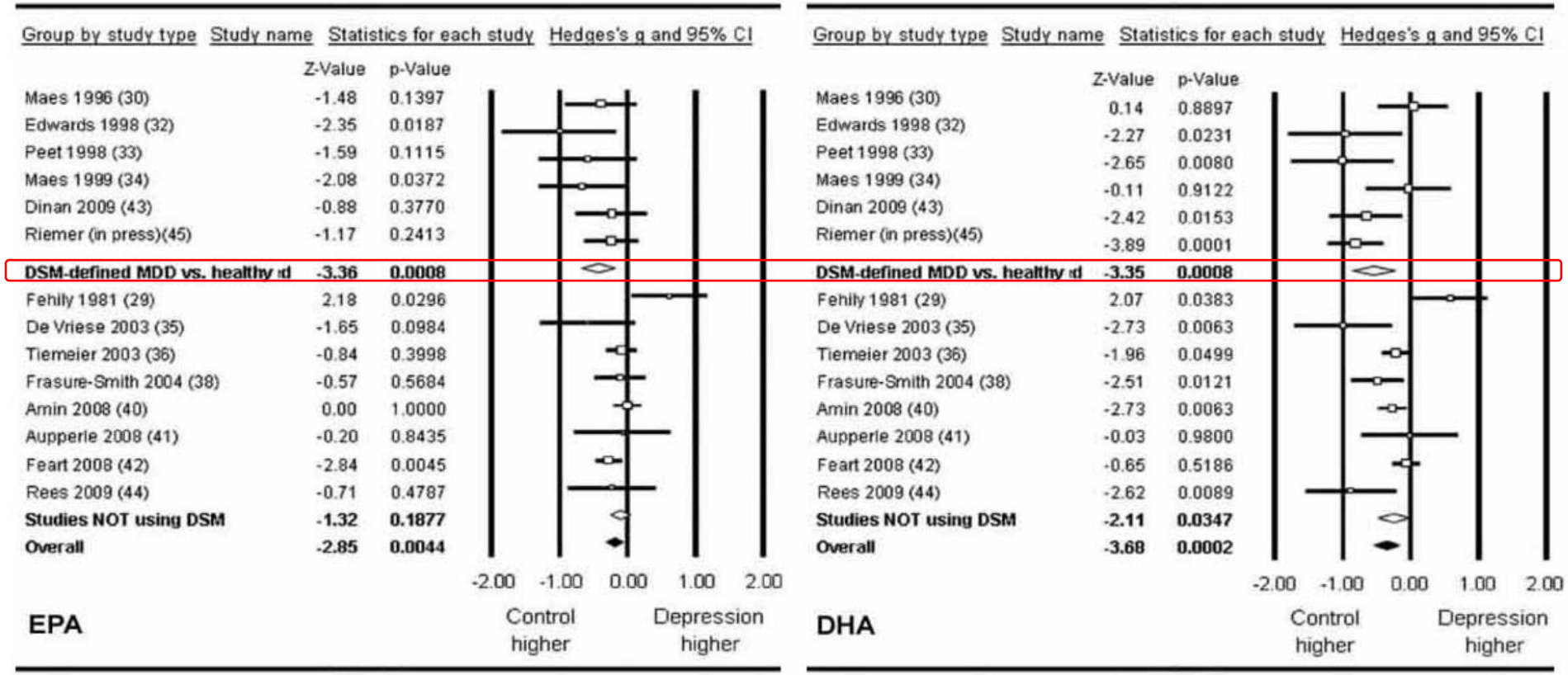


Hibbeln 1998

THE LANCET • Vol 351 • April 18, 1998

OMEGA3(EPA/DHA)於重鬱症患者血中濃度平均值較低

A Meta-Analytic Review of PUFA levels in Patients with Depression. *Lin PY, Huang SY, Su KP. Biol Psych 2010*

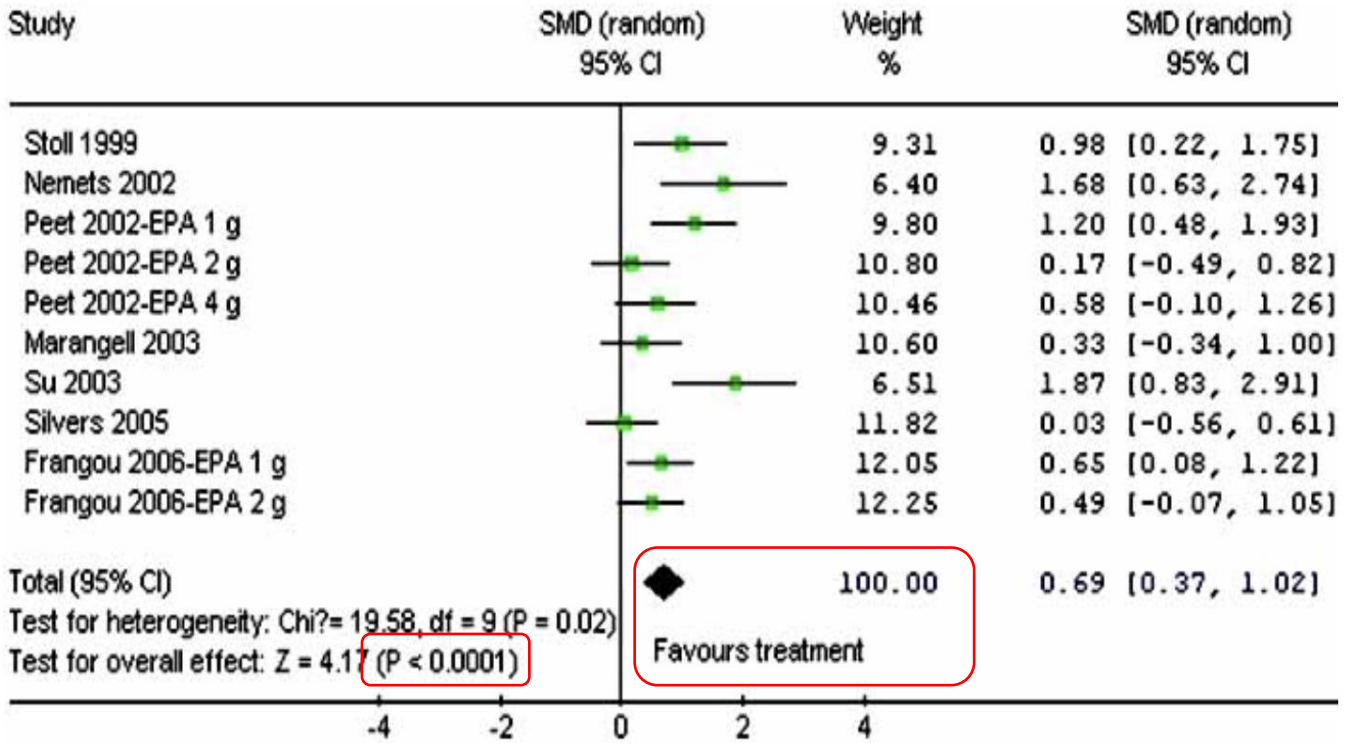


Lin, Huang & Su. Biol Psy 2010

Meta Analysis顯示 Omega-3對於憂鬱症治療有效

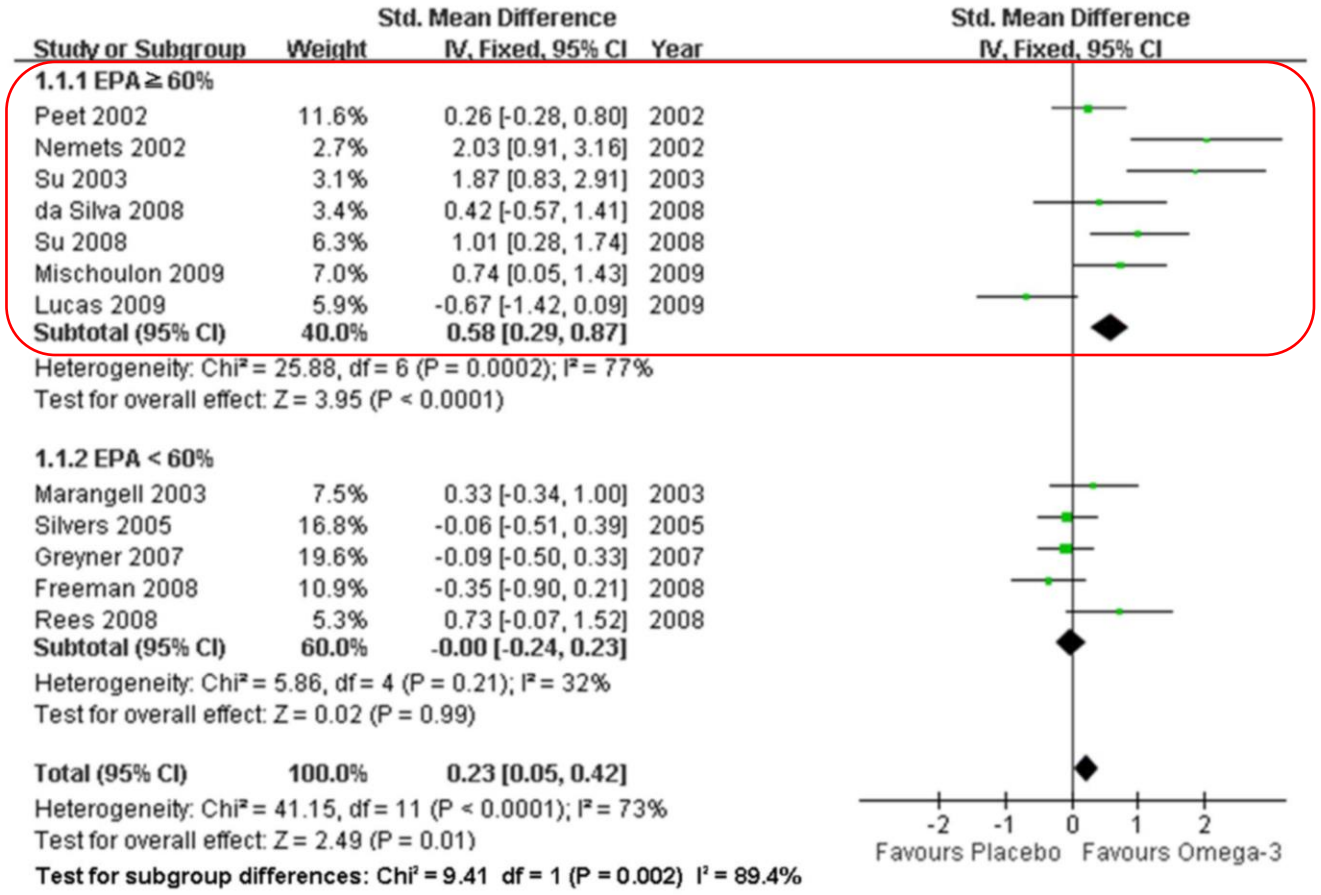
雙盲安慰劑對照組之臨床試驗

Antidepressant effect from controlled trials



Lin & Su. J Clin Psy 2007

Meta-analysis
EPA超過60%
才能改善憂鬱症狀



Lin et al. 2012

怎麼吃魚油才能抗憂鬱？台灣、國際專家訂治療指引

分享 讚大獎 分享 留言 列印 存新聞

2019-09-12 12:31 聯合報 記者羅真／即時報導 讚 126 分享

Dr Kuan-Pin Su

中國醫藥大學身心介面研究中心過去研究發現，深海魚油是治療憂鬱症有效且安全的新療法，為讓醫師與患者精準拿捏劑量，他們召集國際營養精神醫學研究學會（ISNPR）專家小組等專家，共同彙整文獻制訂「Omega-3脂肪酸於憂鬱症治療之臨床指引」，提供臨床醫師參考，也讓憂鬱症患者多一道治療選擇。

Psychotherapy and Psychosomatics

Standard Review Article

Psychother Psychosom
DOI: 10.1159/000502652

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International Society for Nutritional Psychiatry Research Practice Guidelines for Omega-3 Fatty Acids in the Treatment of Major Depressive Disorder

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國際營養精神研究學會(ISNPR)
對於Omega-3於鬱症指引 - 一般原則

(1) 臨床人員在使用 ω-3 PUFAs 治療鬱症病患時，應在進行診斷式會談確認病人疾病診斷、相關心理狀態及身體條件（包括對魚類過敏）。

(2) ω-3 PUFAs 在鬱症治療上，建議配合抗鬱藥物，作為輔助療法（adjunctive therapy）。

(3) 不論作為加速治療（Acceleration，在使用抗鬱劑一開始就同步使用 ω-3 PUFAs）或者做為強化治療（Augmentation，使用抗鬱劑療效不足時才加入 ω-3 PUFAs）皆為安全有效的作法。

(4) 成分與劑量上，建議「單方 EPA」或者「Eicosapentaenoic Acid（EPA）與 Docosahexaenoic acid（DHA）兩者比例大於 2:1 的組合成分」。

(5) 對於鬱症復發的治療上，尚未有足夠證據來支持其療效。

國際營養精神研究學會(ISNPR)
對於Omega-3於鬱症指引 – **急性治療策略**

(6) 每日劑量建議需含有 1–2 g 的 EPA，來源可以是「單方 EPA」或者「EPA 與 DHA 兩者比例大於 2:1 的組合成分」

(7) 對於有沒有療效或者僅有部分療效的患者，兩周後可逐步調高 ω-3 PUFAs 劑量，並可在 4-6 周內視患者的狀況調高到最大劑量。

(8) 對於有沒有療效的患者，建議確認 ω-3 PUFAs 產品品質和濃度。

濃度是影響療效的關鍵!!!

國際營養精神研究學會(ISNPR)
對於Omega-3於鬱症指引 – **復發與預防**

(9) 對於憂鬱症之高風險個案，ω-3 PUFAs 可考慮做為預防性之介入。

(10) 急性治療後，ω-3 PUFAs 也可考慮加入維持治療，降低復發風險。

國際營養精神研究學會(ISNPR)
對於Omega-3於鬱症指引 – **安全性/特殊族群**

(11) 使用高劑量 ω-3 PUFAs 時，建議系統性地評估包含腸胃道、皮膚等的副作用，並且以及完整監測病人的生化及新陳代謝檢驗結果。

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(12) ω-3 PUFAs 可推薦於體重過重（BMI>25）或者體內發炎程度較高的患者。另外對於罹患鬱症的懷孕婦女、兒童、老年人等，ω-3 PUFAs 也可以考慮成為治療選項。

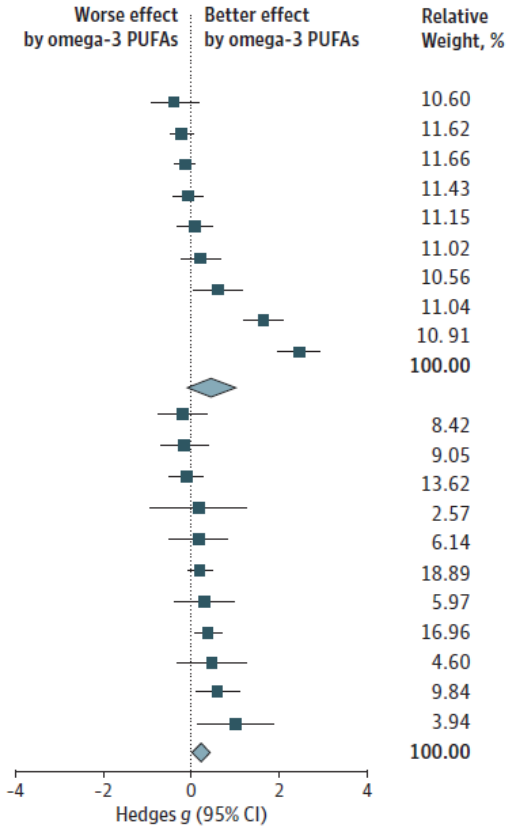
研究發現，以下次族群使用EPA效果比較好

- (一)原本EPA血中濃度低的
- (二)原本體內發炎指數高的
- (三)體重過重(BMI>25)

Anxiety Disorder

- The anxiolytic effect of omega-3 PUFAs was significantly better than that of controls only in subgroups with a higher dosage (at least 2000 mg/d) and not in subgroups with a lower dosage (<2000 mg/d).

Source	Participants, No. Omega-3	Control	Hedges *g* (95% CI)	*P* Value
Dosage <2000 mg/d				
Sauder et al,[55] 2013	26	26	-0.386 (-0.927 to 0.154)	.16
van de Rest et al,[60] 2008	196	106	-0.214 (-0.450 to 0.023)	.08
Cohen et al,[51] 2014	177	178	-0.139 (-0.347 to 0.069)	.19
Cornu et al,[48] 2018	79	81	-0.077 (-0.385 to 0.232)	.63
Widenhorn-Müller et al,[53] 2014	46	49	0.081 (-0.318 to 0.481)	.69
Watanabe et al,[47] 2018	40	40	0.217 (-0.219 to 0.652)	.33
Haberka et al,[35] 2013	26	26	0.610 (0.062 to 1.158)	.03
Yehuda et al,[61] 2005	88	38	1.650 (1.220 to 2.079)	<.001
Sohrabi et al,[56] 2013	63	61	2.459 (1.994 to 2.923)	<.001
Overall			**0.457 (-0.077 to 0.991)**	**.09**
Dosage ≥2000, mg/d				
Sauder et al,[55] 2013	26	26	-0.193 (-0.730 to 0.344)	.48
Freund-Levi et al,[58] 2008	36	24	-0.149 (-0.659 to 0.362)	.57
Matsuoka et al,[49] 2015	53	57	-0.107 (-0.479 to 0.264)	.57
Fux et al,[33] 2004	6	5	0.165 (-0.922 to 1.252)	.77
Bellino et al,[50] 2014	18	16	0.172 (-0.467 to 0.831)	.61
Rogers et al,[49] 2008	109	109	0.200 (-0.065 to 0.465)	.14
Gabbay et al,[57] 2012	17	16	0.306 (-0.364 to 0.976)	.37
Nishi et al,[54] 2013	86	86	0.382 (0.082 to 0.683)	.01
Pomponi et al,[52] 2014	12	12	0.477 (-0.308 to 1.261)	.23
Kiecolt-Glaser et al,[36] 2011	34	34	0.607 (0.126 to 1.088)	.01
Buydens-Branchey et al,[34] 2008	11	11	1.010 (0.153 to 1.868)	.02
Overall			**0.213 (0.031 to 0.395)**	**.02**



JAMA Network Open. 2018;1(5):e182327

Bipolar Disorder

- Low levels of omega-3 fatty acids, in erythrocyte membranes have been found in individuals with this disorder. (C.C. Chiu, S.Y. Huang, K.P. Su, et al.2006)
- Therapeutic trials on the effects of omega-3 PUFA administration on bipolar disorder have yielded variable results.
- The conclusions of systematic reviews and meta-analyses serve as preliminary evidence for the contention that the depressive but not manic symptoms of bipolar disorder can be improved through the adjunctive administration of omega-3 PUFAs. J Clin Psychiatry, 73 (1) (2012)

Schizophrenia

- Deficiencies of several micronutrients, including essential fatty acids, folate, iron, and vitamin D, during prenatal development, are potential risk factors for schizophrenia. Schizophr Bull, 34 (6) (2008)
- The findings of intervention trials are inconsistent.
- Omega-3 PUFAs may be more effective in treating schizophrenia when they are administered during the early stages of the disorder than during the chronic phase. This may be attributable to the neuroprotective effects. Ann Clin Psychiatry, 27 (4) (2015)
- Omega-3 PUFAs may be able to ameliorate the motor side effects (extrapyramidal symptoms, tardive dyskinesia) of classical antipsychotics. Schizophr Res, 84 (1) (2006)

Other mental disorders

- Obsessive-compulsive disorder
- Posttraumatic stress disorder
- Personality disorders who frequently exhibit high levels of aggressiveness and impulsive-behavioral dyscontrol (borderline personality disorder)
- Perinatal depression

Perinatal depression

- Recommendations for pregnant women include 1 or 2 portions of oily fish weekly or 200 mg DHA per day .
- Studies have provided promising preliminary data regarding feasibility, tolerability, and efficacy in perinatal depression.
- Based on positive findings from RCTs and meta-analyses in non-perinatal depression, we recommend perinatal patients with depression should consume 1 gram EPA + DHA daily. (KM Deligiannidis et al., *Best Pract Res Clin Obstet Gynaecol* 2014)

孕婦使用高劑量EPA真的安全嗎？

2016 NEJM大型臨床實驗發現，懷孕第24週婦女補充高劑量N-3(含EPA1.32g/DHA0.88g)至分娩，安全性與安慰劑無異！且能降低新生兒32%下呼吸道感染及氣喘率!!

(1)RCT

(2)N=736 pregnant women at 24 weeks

(3)to receive
2.4 g of n−3(**EPA 1.32g** + DHA0.88g)
or placebo (olive oil)

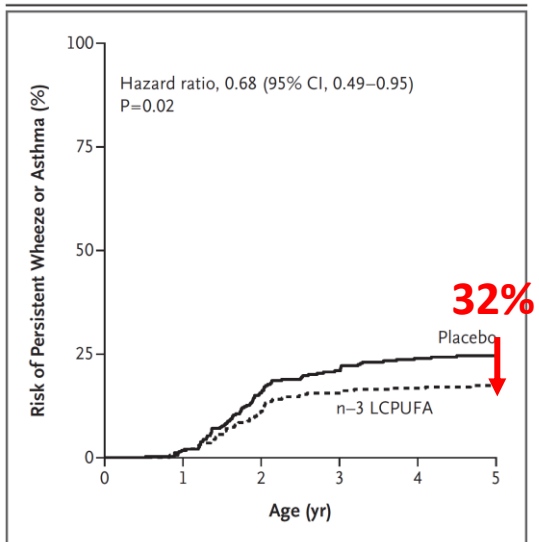
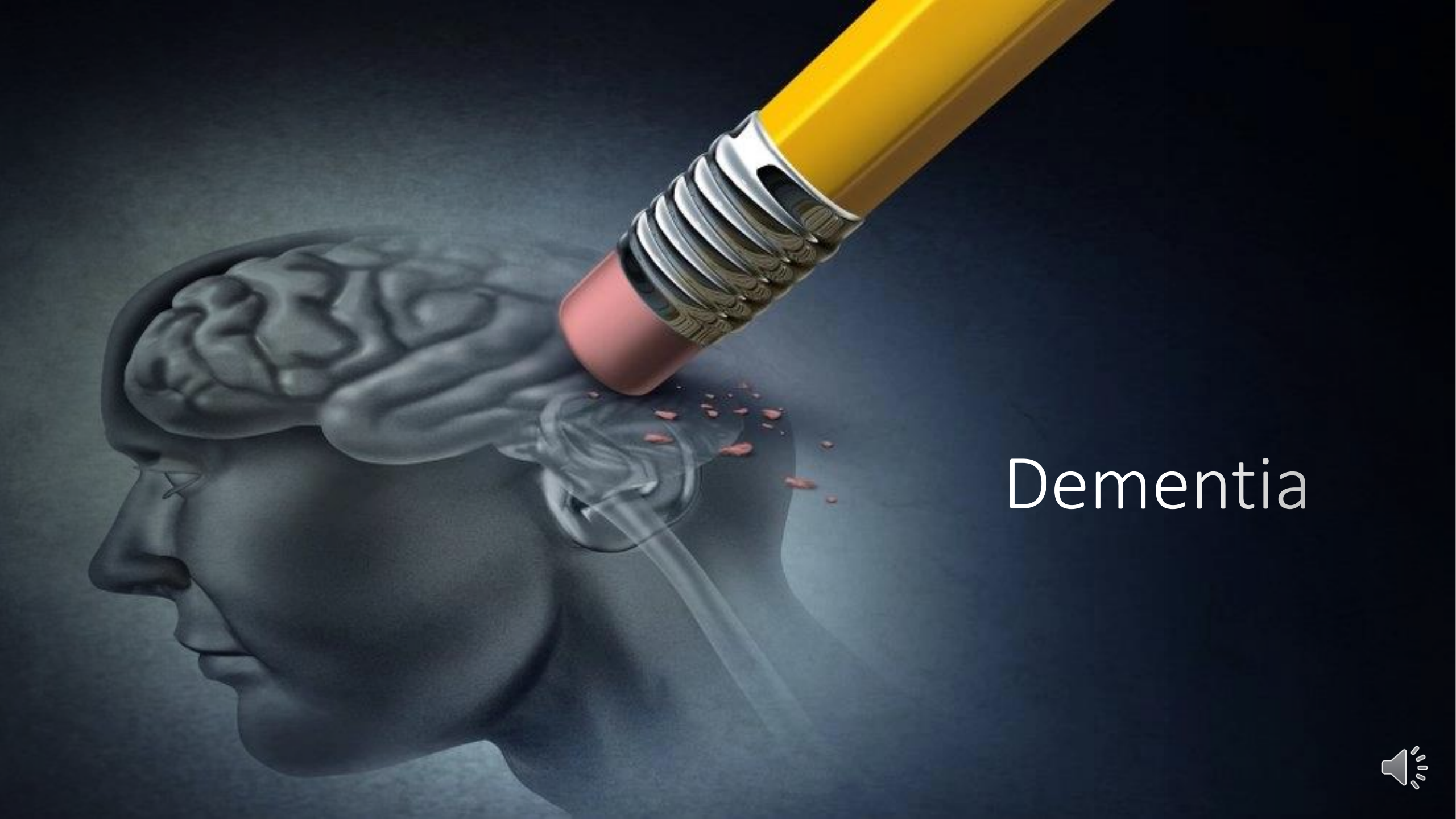


Figure 1. Risk of Persistent Wheeze or Asthma in Children According to n–3 LCPUFA Supplementation or Placebo during Pregnancy.
LCPUFA denotes long-chain polyunsaturated fatty acids.

Table S7
Safety assessment in the $COPSAC_{2010}$ pregnancy cohort.

	Randomization % (N)		P-value
Adverse Events	**n-3 LCPUFA**	**Control**	
	49.6% (365)	**50.4% (371)**	-
Maternal/pregnancy			
Death	0% (0)	0% (0)	-
Intrauterine death	0.6% (2)	0.5% (2)	0.99
Gestational diabetes	1.7% (6)	2.9% (10)	0.32
Preeclampsia	4.6% (16)	4.3% (15)	0.83
Days hospitalized after birth, mean (SD)	2.9 (2.6)	2.7 (2.8)	0.48
Mother hospitalized >5 days	9.6% (32)	9.5% (33)	0.99
Emergency caesarean section	14.3% (52)	10.8% (40)	0.16
Antibiotics in third pregnancy trimester	18.9% (66)	17.5% (62)	0.63
Infection in third pregnancy trimester	27.8% (96)	33.5% (118)	0.10
Infant			
Death	0% (0)	0% (0)	-
Extremely preterm (<28 weeks) birth	0.3% (1)	0.3% (1)	0.99
Very preterm (28 to <32 weeks) birth	0.6% (2)	0.8% (3)	0.67
Moderate to late preterm (32 to <37 weeks) birth	3.3% (12)	3.8% (14)	0.72
Child hospitalized after birth	11.7% (41)	11.2% (40)	0.85
Any congenital malformation	5.2% (19)	6.2% (23)	0.56

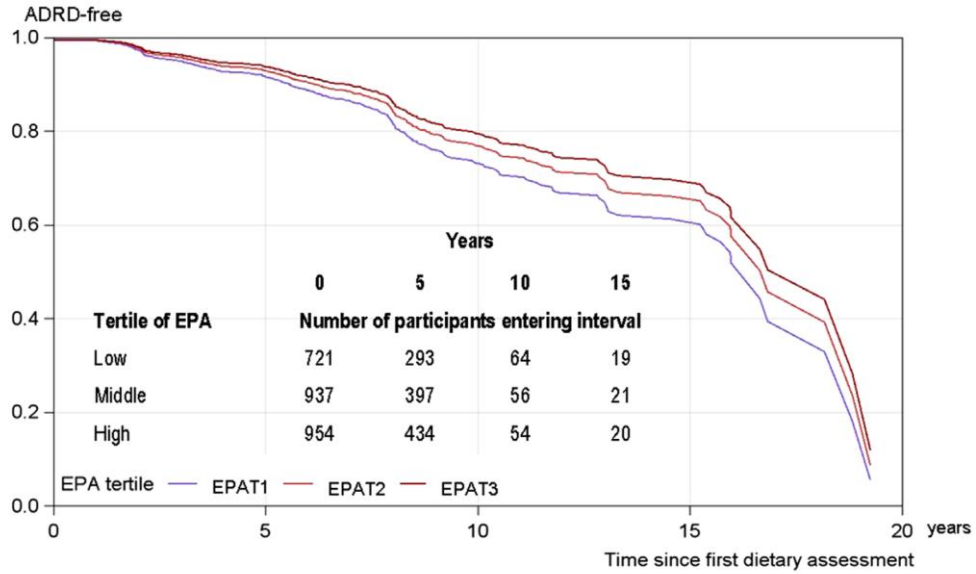
N Engl J Med 375;26 nejm.org December 29, 2016

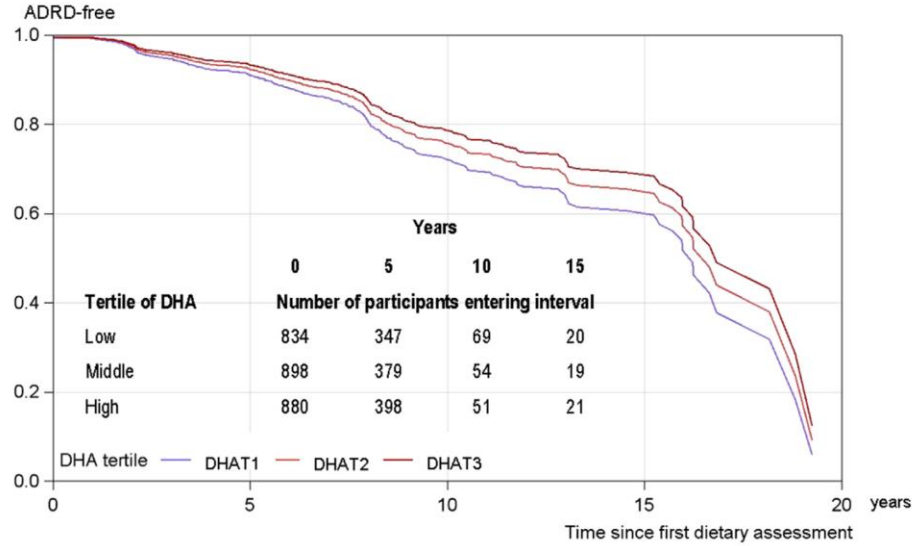


Dementia

2020大型觀察性研究發現，老年人Omega-3攝取量與dementia發生率呈負相關

(1)Prospective observational study of aging and dementia among **elderly(≥ 65 years)**
(2)2612 multiethnic women (67%) and men (baseline age 76.3 [6.4] years),





Alzheimer's Dement. 2020;1–12.

Dementia

- Omega-3 fatty acid supplementation did not significantly influence dementia risk.
- The inconsistent results may be attributable to variability in cohort characteristics dosages, treatment durations, and outcome measures among the included studies.
- Beneficial effects only during the premorbid or early stages of the disease, particularly among noncarriers of the apolipoprotein *E*-ε4 risk gene. Alzheimers Dement, 11 (2) (2014)
- The overall composition of fatty acid intake may be more important to cognitive aging than the amount of omega-3 fatty acids consumed or total fat intake. Ann Neurol, 72 (1) (2012)
- The consumption of saturated and trans fatty acids may affect cognition and increase the risk of developing Alzheimer's disease and consequently mask the benefits of dietary PUFAs. Curr Alzheimer Res, 8 (5) (2011)
- The oxidization of omega-3 PUFAs may alter their biological function and even result in harmful effects. Sci Rep, 5 (2015)

2021蘇教授研究團隊發現，
給予失智症患者補充Omega-3(EPA/DHA)在語言表達上有些微幫助

上報 | 9.6k 人追蹤 ☆ 追蹤

中醫大研究發現補充Omega-3有助減少失智症患者認知缺損

楊文琳

2021年11月8日 · 1 分鐘 (閱讀時間)

高齡失智症造成病人和家屬極大的衝擊，其中最主要的阿茲海默症至今尚未發現有效治癒的藥法；中國醫藥大學跨醫院研究團隊發現，Omega-3脂肪酸的補充有助於減少阿茲

Dr Kuan-Pin Su

Conclusion: Overall, **n-3 PUFAs supplements did not reduce cognitive, functional, and depressive symptom outcomes, but spoken language ability and constructional praxis subitems of ADAS-cog.** These findings show that attention to clinical heterogeneity in dementia is crucial when studying nutrients interventions, such as n-3 PUFAs. In addition, with small effect size CCL4 is a better indicator than other inflammatory cytokines for EPA treatment response.

(1)N= 163 MCI or AD patients
(2)DHA 0.7g + EPA 1.6g or DHA 0.35g + EPA 0.8g or Placebo

Brain Behav Immun . 2021 Oct 29;99:289-298.

補充Omega-3能幫助健康中老年人提升行為執行力及語言流利度，且語言流利度的增進與EPA血中濃度有關！

(1)RCT
(2)65 healthy subjects(50–75 years)
(3) 2.2 g/day LC-n3-FA or placebo 26 weeks

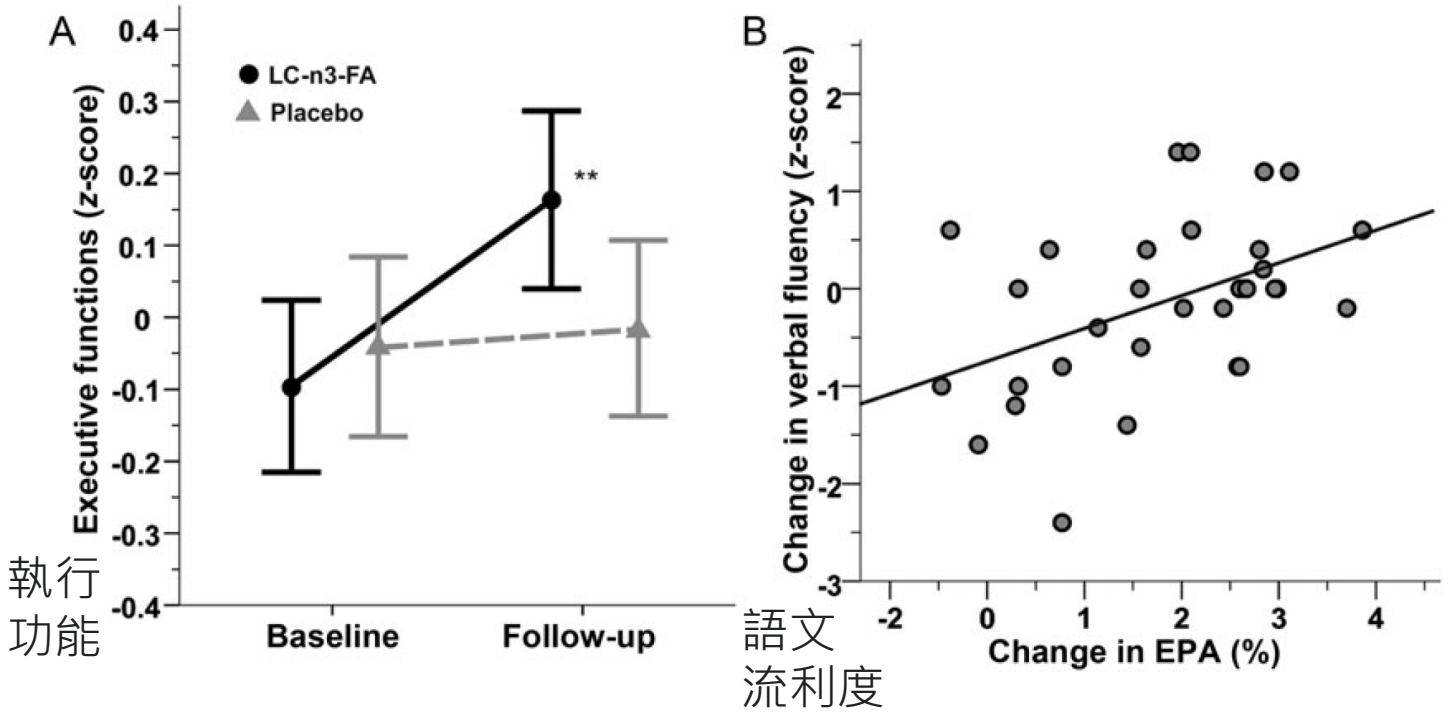
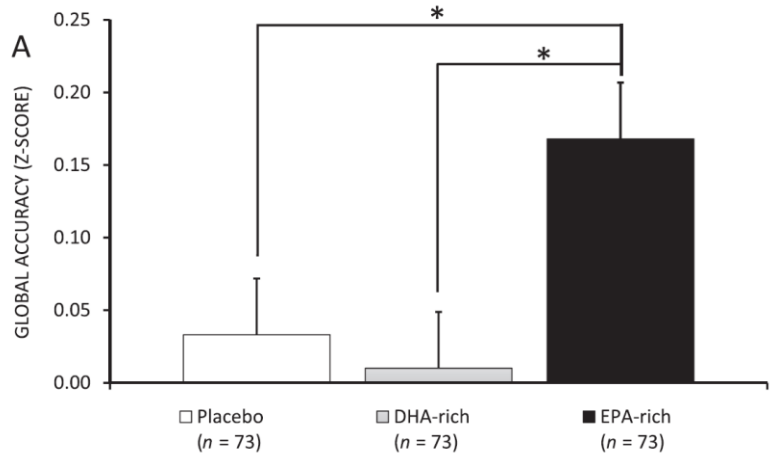


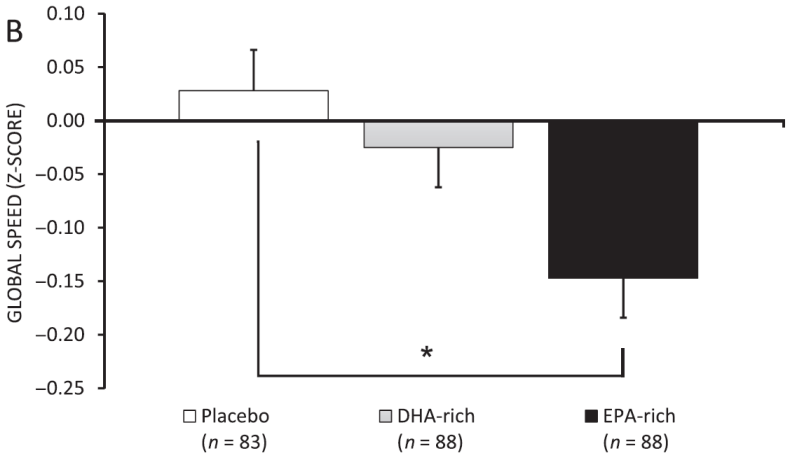
Figure 3. Changes in executive functions due to 26 weeks of supplementary LC-n3-FA or placebo. (A) Subjects of the LC-n3-FA-group (black, circles) significantly improved in executive functions compared with controls (dashed, triangles, ANOVARM, P=0.023, Bonferroni-corrected). (B) Improvements in a subtest of executive functions, that is verbal fluency, correlated significantly with increases in EPA content in the membranes of erythrocytes after LC-n3-FA supplementation (P=0.009). Error bars indicate standard error.
**P<0.01 according to post hoc t-test.

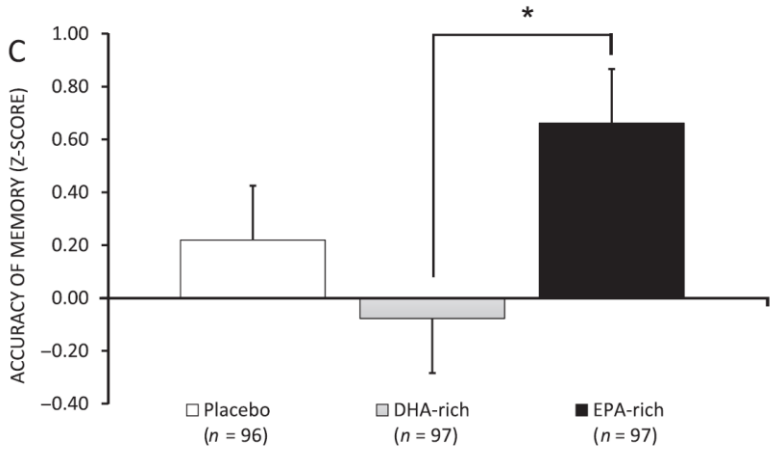
Cereb Cortex. 2014 Nov;24(11):3059-68.

EPA的補充能增進健康青壯年智能相關表現
DHA沒有統計差異

(1)26-wk RCT
(2)Healthy adults (*n* = 310; age range: 25–49 y)
(3)900mgEPA + 360mgDHA (EPA rich)
900mgDHA + 270mgEPA (DHA rich)
Refined olive oil (placebo)







Am J Clin Nutr 2021;00:1–11.

EPA對於健康人智能表現的影響>DHA
此結果與目前ADHD研究結果雷同

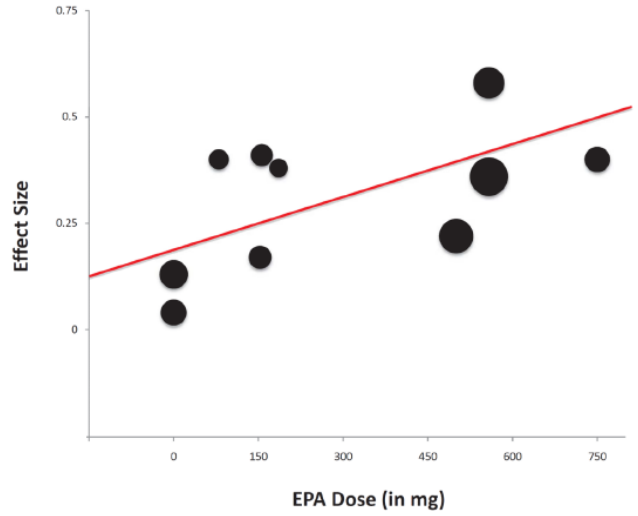
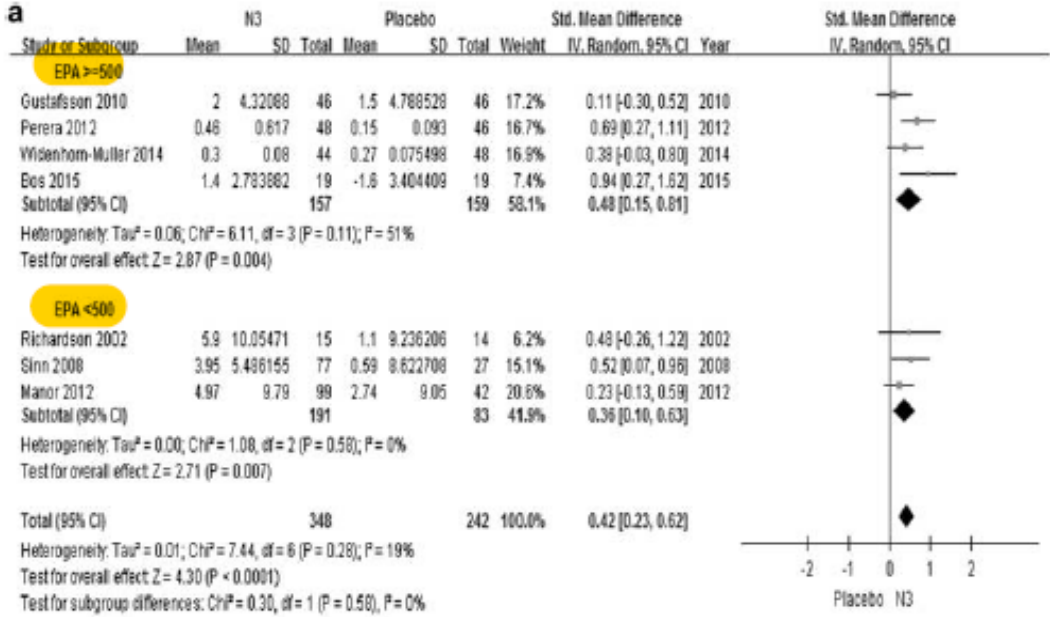


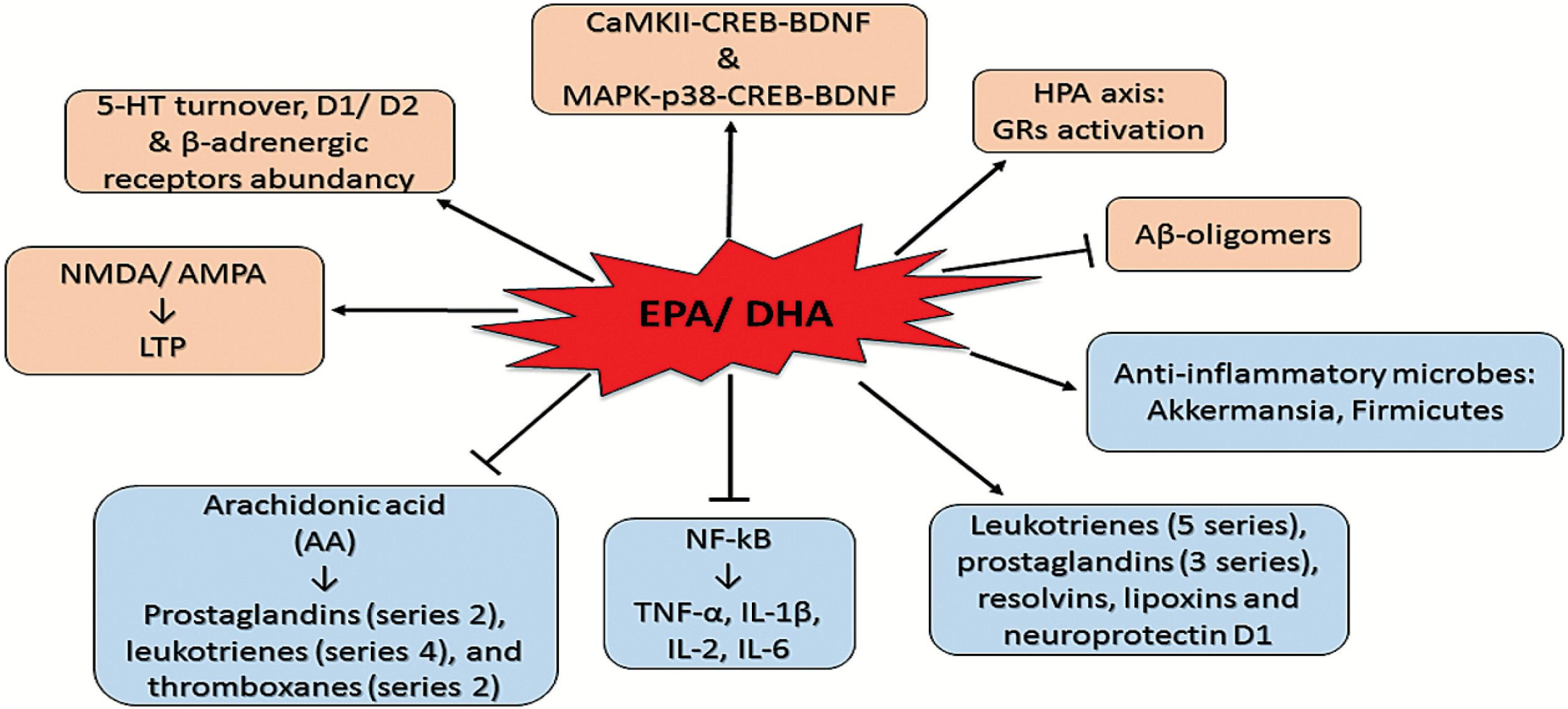
Figure 3. Eicosapentaenoic acid dose and Efficacy of Omega-3 Fatty Acid Supplementation for Attention-Deficit Hyperactivity Disorder (ADHD)

J Am Acad Child Adolesc Psychiatry. 2011 Oct;50(10):991-1000.



Neuropsychopharmacology (2018) 43, 534–545

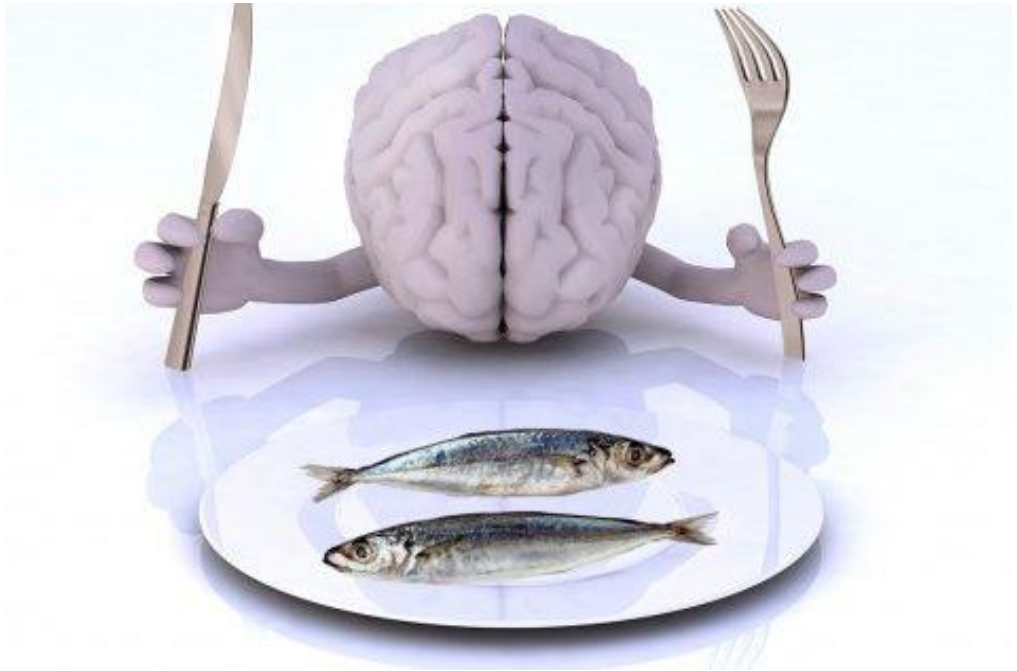
Figure 2. Omega-3 polyunsaturated fatty acid [(n-3) PUFA] mechanisms of action.



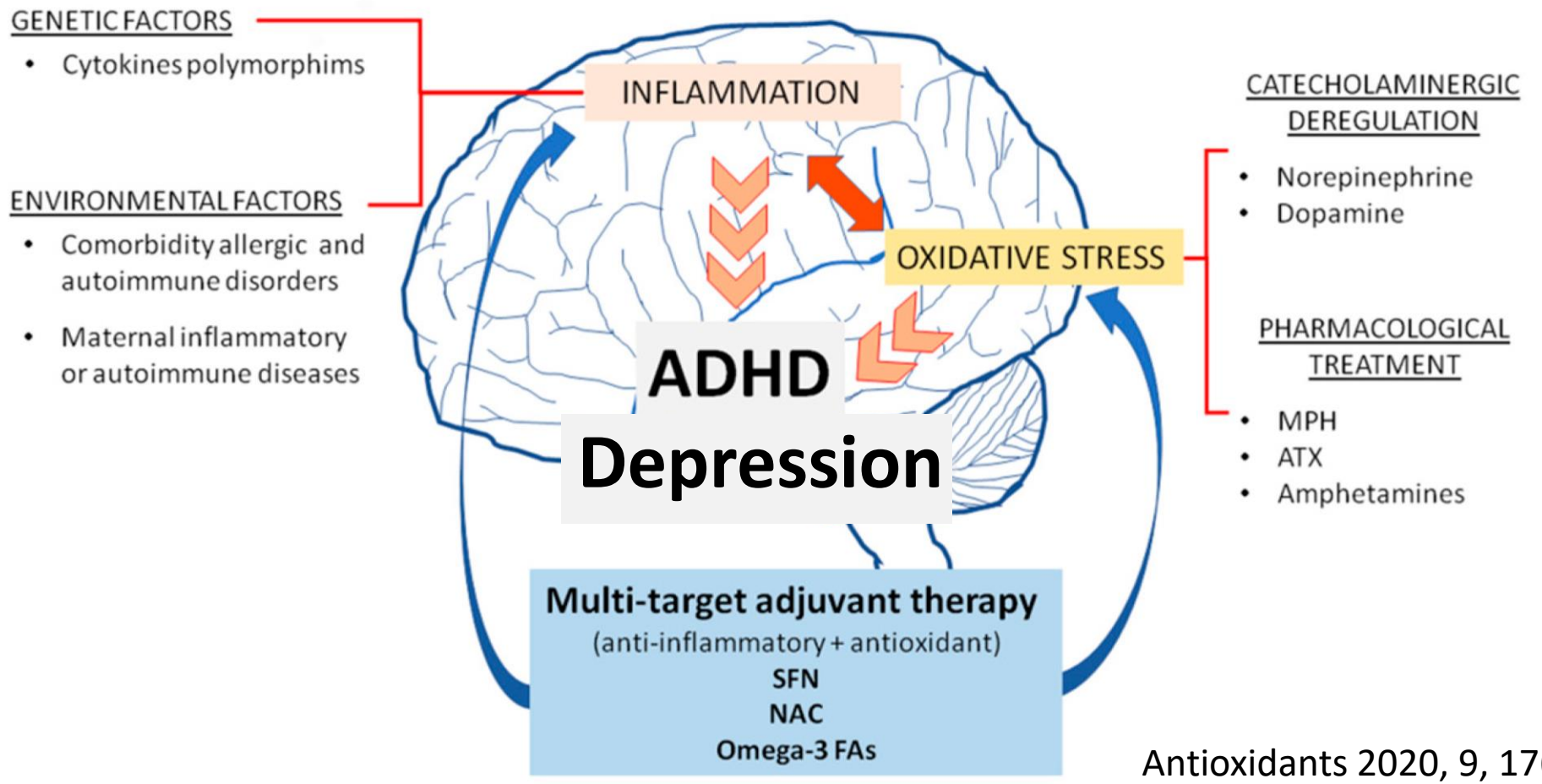
Int J Neuropsychopharmacol. 2016 Dec 30;19(12):pyw078.

Omega-3 Fatty Acids : Mechanisms of Action

- Inflammation
- HPA Axis
- BDNF
- Monoaminergic System
- Glutamatergic System
- Aβ Oligomers and Antiapoptosis
- New Horizons: The Gut Microbiome

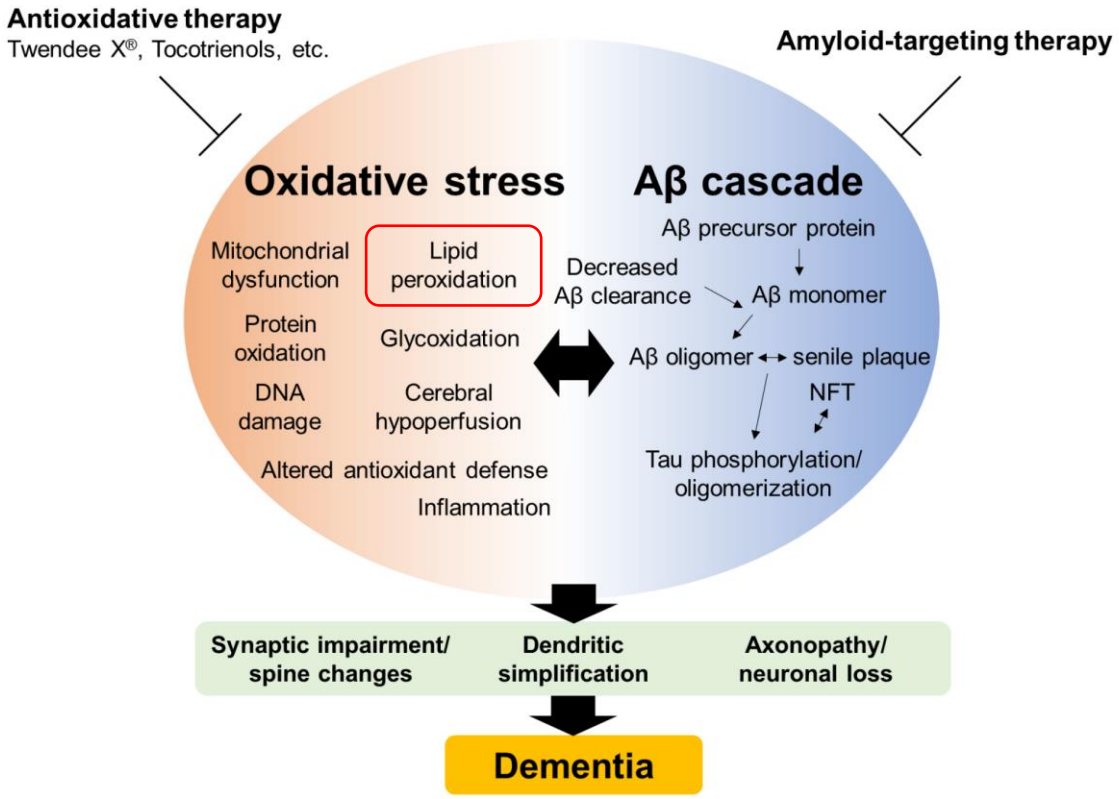


為何EPA對於身心疾病及智能有幫助？
Anti-inflammatory + antioxidant

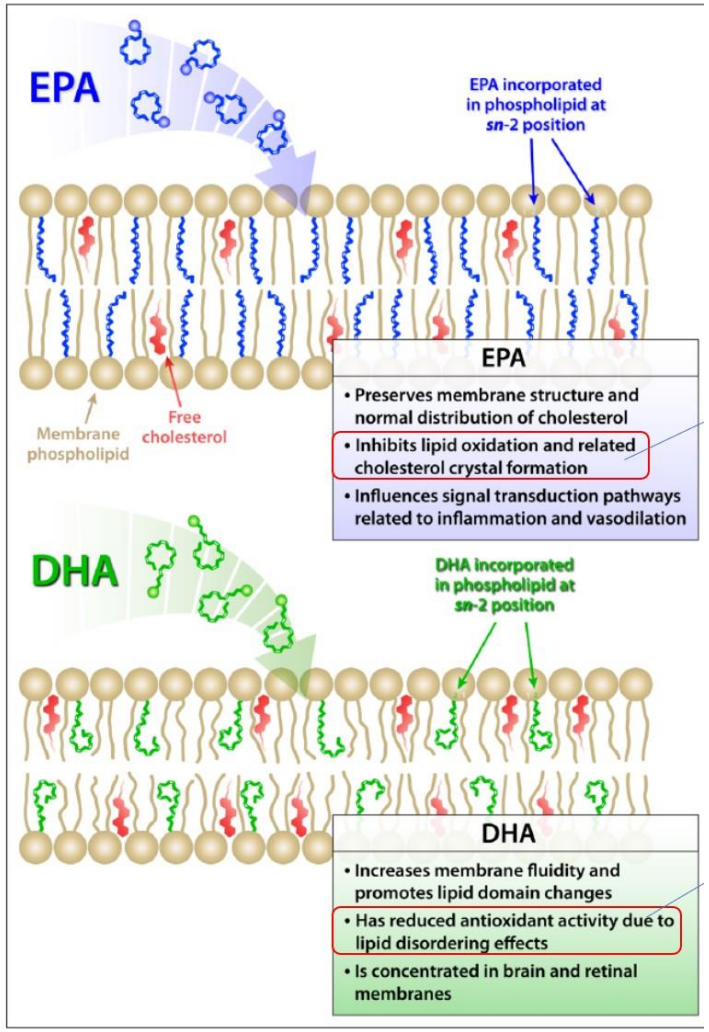


Antioxidants 2020, 9, 176

脂質的氧化也是大腦氧化壓力來源之一，僅EPA能有效抑制脂質氧化!



Int. J. Mol. Sci. **2020**, 21, 1974



Current Atherosclerosis Reports (2019) 21: 2

Other clinical implications:

- Obesity
- Metabolic syndrome
- Infertility & PCOS
- headache reduction in adults with migraine
- Omega-3 fatty acids in immune health
- Omega-3 Fatty Acids in Rheumatic Diseases
- Omega-3 Fatty Acids and Cancer Cell Cytotoxicity: Implications for Multi-Targeted Cancer Therapy
- COVID-19 and Omega-3 nutrition

Long COVID and OMEGA-3 PUFAs

Brain Behav Immun. 2022 Jul

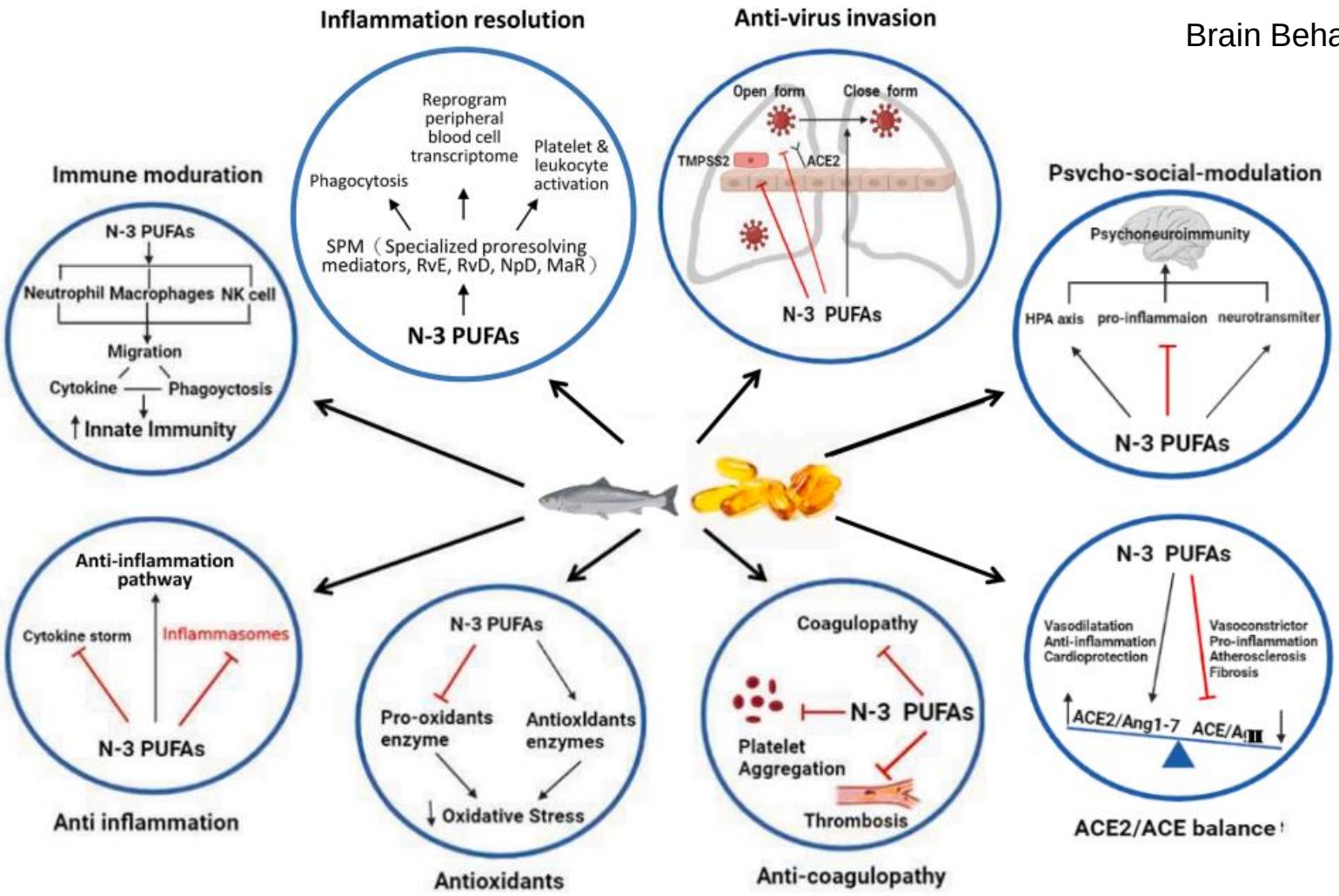


Fig. 2. The summary of potential molecular mechanisms of omega-3 polyunsaturated fatty acids on long COVID. ACE: Angiotensin-converting enzyme; HPA: hypothalamus-pituitary-adrenal; MaR: maresin; n-3 PUFAs: Long chain omega-3 polyunsaturated fatty acids; NpD: neuroprotectin D; RvD: resolvin D; RvE: resolvin E.

Adverse effects of omega-3 PUFA supplementation

- Common adverse effects of fish-oil preparations include nausea, fishy belching, and loose stools.
- In general, omega-3 PUFAs do not seem to have clinically relevant effects on bleeding time.
- Contamination: methylmercury, dioxins, and polychlorinated biphenyls
- Fish-oil supplements may contain antioxidants and omega-3 PUFAs oxidation products, both of which can lead to adverse reactions.
- The possible adverse consequences of the long-term use of vitamin E.

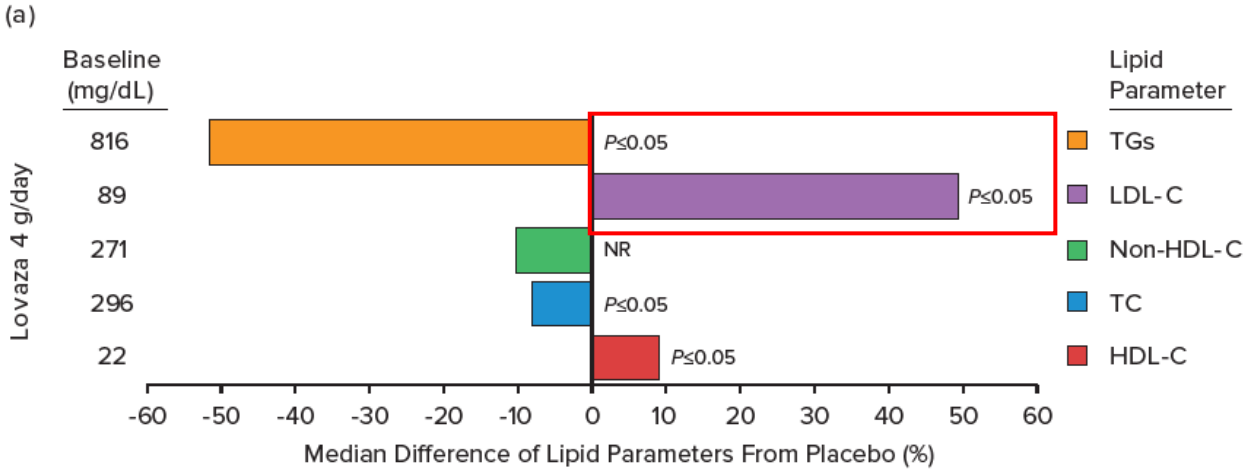
Conclusion

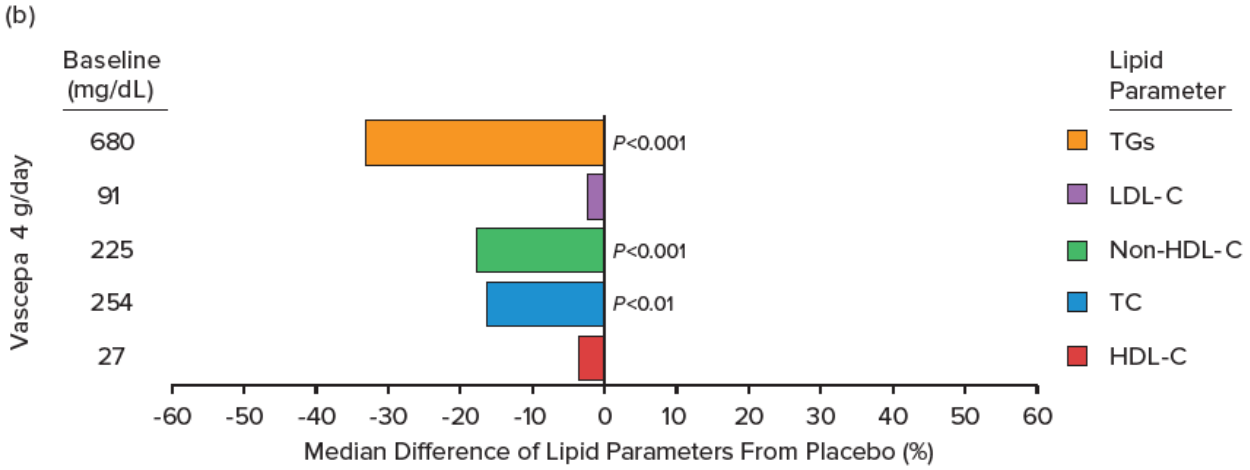
- Recent evidence supports the importance of n-3 PUFAs in brain functioning and the action of their supplementation in psychiatric disorders.
- Mechanisms of the potential preventive and therapeutic effect of n-3 PUFAs is still unclear. (Anti-inflammatory + antioxidant)
- Challenges to examine the effects of omega-3 fatty acids : identifying subgroups of individuals , useful composition, optimal dosages, duration of supplementation, and critical phases of brain development.
- The undesirable side effects of omega-3 fatty acid supplementation should be examined. (contamination, PUFA oxidation products, or added vitamin E.)

臨床觀察到混合型N-3(DHA/EPA)會提升LDL-C，但純EPA魚油不會 (DHA專一副作用)

(EPA460mg/DHA380mg)
美國混合型魚油處方藥

(EPA1000mg)
美國純EPA處方藥





P&T® • December 2015 • Vol. 40 No. 12

OMEGA-3發現與現行降TG藥物療效差不多

Table 12. Effect of Lipid-Lowering Therapies on Triglyceride Reduction[504,480a–480d]

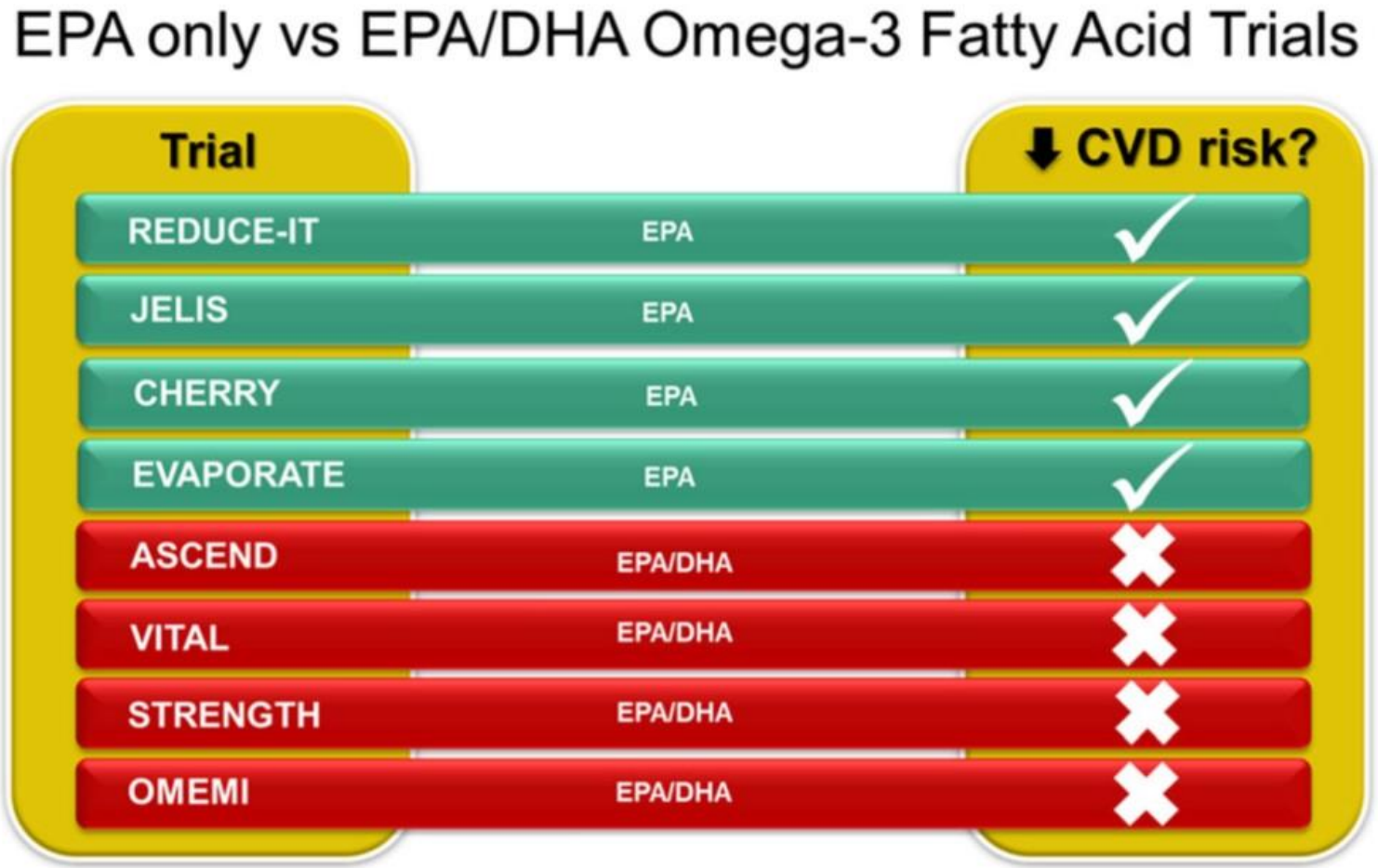
Drug	% Triglyceride Reduction
Fibrates	30–50
Immediate-release niacin	20–50
Omega-3	20–50
Extended-release niacin	10–30
Statins	10–30
Ezetimibe	5–10

降三酸甘油脂為主藥物

降膽固醇為主藥物

Circulation. 2011;123:2292-2333.

近10年大型臨床實驗告訴我們，只有純EPA才能有效預防心臟病/中風的發生(無論初次/二次預防)



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總結

(一)EPA建議用於：

憂鬱、焦慮、過動、認知功能障礙等族群

(二)有以下合併症更適合 !!!

任何炎症(乾眼症/鼻炎/氣喘/皮膚炎/關節炎)

高心血管疾病風險族群

(三高/肥胖/抽菸/已罹患心血管疾病)

(三)EPA 建議劑量:

- 憂鬱/焦慮症：1~2g/天
- 過動症：≥0.5g/天
- 認知功能障礙：≥0.9g/天
- 高三酸甘油脂：1~4g/天
- 預防心臟病/中風：≥2g/天