Nutrition Research Reviews (2008), **21**, 13–41
doi:10.1017/S0954422408998620

Is there a role for *n*-3 long-chain polyunsaturated fatty acids in the regulation of mood and behaviour? A review of the evidence to date from epidemiological studies, clinical studies and intervention trials

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Selected biochemical evidence suggests a potential role for *n*-3 long-chain PUFA (*n*-3PUFA) in the regulation of mood and behaviour. The present paper reviews the relevant evidence, to date, from epidemiological studies, clinical studies and intervention trials. Most evidence is available investigating a role for *n*-3PUFA in depression, depressive illness and suicidal behaviour, but work is also available on anxiety and anxiety-related disorders, fatigue and fatigue-related disorders, aggression, hostility and anti-social behaviour, inattention, impulsivity and attention deficit hyperactivity disorder and schizophrenic disorders. For all these aspects of mood and behaviour, the evidence available is currently limited and highly inconsistent, both in terms of study methodology and study findings. There is a clear need for further work in this area.

***n*-3 Long-chain polyunsaturated fatty acids: Mood: Behaviour**

Introduction

Increasing interest surrounds the possibility that *n*-3 long-chain PUFA (*n*-3PUFA) may be implicated in the regulation of mood and behaviour. This interest stems from evidence of effects of *n*-3PUFA on cell membrane structure and function, and early evidence suggesting a role for *n*-3PUFA in the development and/or treatment of various disorders of mood and behaviour. More recent evidence, however, questions the robustness of this early evidence. The present paper aims to provide a comprehensive review of the evidence to date investigating a role for *n*-3PUFA in the regulation of mood and behaviour.

n-3 Long-chain polyunsaturated fatty acids

n-3PUFA (also named omega-3 fatty acids) are a family of PUFA, named as such due to the positioning of the first double carbon bond on the third atom from the methyl end of the acyl chain. All members of the family are derived from the parent fatty acid 18: 3*n*-3 (α-linolenic acid (ALA)), via desaturation and elongation[1,2], as demonstrated in Fig. 1. Closely related to the *n*-3PUFA are the *n*-6 long-chain PUFA (*n*-6PUFA), named from the positioning of the first double bond on the sixth carbon atom from the methyl end of the acyl chain. *n*-6PUFA are derived from the parent fatty acid 18 : 2*n*-6 (linoleic acid), and for synthesis share the same desaturases and elongases as *n*-3PUFA. The *n*-3 and *n*-6PUFA thus compete for synthesis from their parent fatty acids. The parent fatty acids, however, cannot be synthesised by man[1,2].

As essential fatty acids, ALA and linoleic acid must be obtained from the diet. Longer-chain *n*-3 and *n*-6PUFA can be formed in man, but biological conversion is slow and inefficient, making diet an important source for these fatty acids as well[3]. Dietary sources of ALA include certain nuts and seeds, such as walnuts, flaxseed and rapeseed oil, and dietary sources of the longer *n*-3PUFA EPA and DHA include fatty fish, some white fish, shellfish and other seafoods such as seaweed, and certain eggs and animal products dependent on the animals' diet[2,4–6]. Dietary sources of linoleic acid and all *n*-6PUFA include plant and vegetable seeds and oils, as found in margarines and the majority of processed foods[5,6]. Dietary intakes of *n*-3 and *n*-6PUFA, however, have changed dramatically over recent decades. Our traditional diet is thought to have contained approximately equal amounts of energy from *n*-3PUFA and *n*-6PUFA[6]. By comparison, a current

Abbreviations: ADHD, attention deficit hyperactivity disorder; ALA, α-linolenic acid; E-EPA, EPA ethyl ester; 5-HT, 5-hydroxytryptamine; *n*-3PUFA, *n*-3 long-chain PUFA; *n*-6PUFA, *n*-6 long-chain PUFA.

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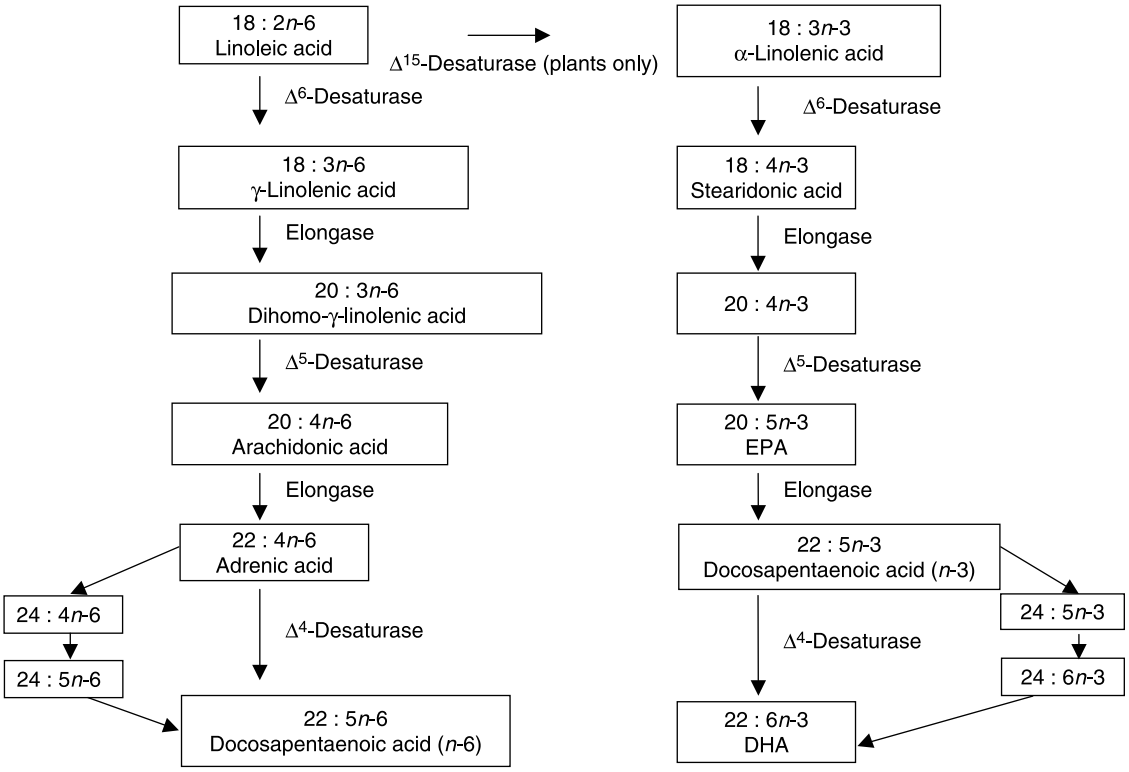

Fig. 1. Desaturation and elongation of *n*-3 long-chain PUFA.

Western diet is estimated to contain approximately five to twenty times more energy from *n*-6PUFA than from *n*-3PUFA[6,7]. The increasing imbalance between *n*-3 and *n*-6PUFA is currently thought to impact on cell membrane structure and function.

n-3 Long-chain polyunsaturated fatty acids in cell membrane structure and function

Both *n*-3 and *n*-6PUFA are integral components of all cell membranes as part of the phospholipid bilayer. Within the phospholipid bilayer, *n*-3PUFA and *n*-6PUFA can be interchanged, where incorporation into the membrane depends largely on PUFA availability, both from the diet and from chemical synthesis[1,2,5]. Incorporation into cell membranes, dependent on availability, has been clearly demonstrated[8,9]. Membrane composition, however, affects membrane function. First, *n*-3PUFA molecules, due to their size and shape, influence the physical state of the membrane, resulting in increased fluidity and permeability. Ehringer *et al.* [10] found DHA administration to result in increased permeability of the phospholipid bilayer *in vitro*, Tappia *et al.* [11] found supplementation with fish oil to result in increases in membrane fluidity in rats and Hirashima *et al.* [12] found supplementation with *n*-3PUFA to result in a decrease in T_2 values (brain water proton transverse relaxation times) indicative of increased membrane fluidity in humans. This increased fluidity may aid cross-cell membrane transport, aiding cell communication and functionality[1].

Second, *n*-3 and *n*-6PUFA are also thought to have different effects on surrounding molecules and cell functions. Specifically, *n*-3 and *n*-6PUFA are considered important in cell signalling and signal transduction[1,2,5]. *n*-3 and *n*-6PUFA are thought to impact directly on the activity of a number of enzymes in various neurotransmitter pathways, resulting in changes in the activities of these systems[1]. *n*-3PUFA-deficient diets have been associated with lower levels of serotonin and dopamine in piglets[13]. In rats, *n*-3PUFA-deficient diets have been found to result in increased serotonin 5-HT_2 receptor density in the frontal cortex[14,15], elevated 5-HT_{2A} receptor binding density in the prefrontal cortex[16], lower levels of dopamine in the cortex, hippocampus and striatum[14,15,17], a decreased density of D_2 receptors in the frontal cortex[14,15], reduced D_2 receptor binding density in the prefrontal cortex[16], decreased activity in the mesocortical dopamine pathway and increased activity in the mesolimbic dopamine pathway[18], and higher levels of noradrenalin in the cortex, hippocampus and striatum[17], compared with control diets. Supplementation with *n*-3PUFA has also been found to result in enhanced 5-HT responsivity[19] and reductions in noradrenalin[20,21] in humans.

n-3 and *n*-6PUFA are also thought to affect enzymes which result in the release of fatty acids from the phospholipid bilayer to form a number of eicosanoids, prostaglandins and leucotrienes. These compounds can have effects on signal transduction, resulting again in increased activity and increased cell signalling[1,2,5]. These compounds can also have either pro- or anti-inflammatory

https://doi.org/10.1017/S0954422408998620 Published online by Cambridge University Press

properties depending on their derivation – prostaglandins formed from the *n*-6PUFA arachidonic acid are typically pro-inflammatory, prostaglandins formed from EPA are typically anti-inflammatory[2,5,22]. Supplementation with EPA has been found to result in reduced production of inflammatory cytokines in animals and in humans[5,22]. Low levels of docosapentaenoic acid *n*-3 in human erythrocyte membranes have also been associated with high levels of the pro-inflammatory cytokine IL-6[23], and supplementation with ALA has been found to result in reductions in inflammatory cytokines – TNFα and IL-1β[24], and reductions in IL-6, C-reactive protein and serum amyloid A[25].

n-3 and *n*-6PUFA have also been found to modulate ion channels important in cell signalling and transmission. Ion transfer is vital for neurotransmission, and *n*-3PUFA have been associated with an inhibition of enzymes that maintain ion gradients[26]. Deficiencies in dietary ALA have also been found to result in a reduction of neural enzyme activity in the rat brain[27], and deficiencies in dietary DHA have been found to result in decreased neuron size in several areas of the rat brain[28], diminished nerve growth factor levels in the hippocampus and increased nerve growth factor in the piriform cortex[29].

The serotonergic, dopaminergic and adrenergic neurotransmitter systems are known to be important in the regulation of mood and behaviour[1]. The anti-inflammatory effect of *n*-3PUFA are also thought to be important in a number of behavioural conditions[5]. The biochemical evidence thus suggests a potential role for *n*-3PUFA in the regulation of mood and behaviour, and has resulted in the development of a number of hypotheses centring around a role for *n*-3PUFA in a number of mood and behavioural conditions. These hypotheses include the biogenic amine hypothesis of depression[30], the immune/inflammatory hypothesis of psychiatric disease[31] and the membrane hypothesis of schizophrenia[32].

While biochemical work continues to examine these various hypotheses, epidemiological, clinical and trial evidence investigating a role for *n*-3PUFA in the regulation of mood and behaviour is also available.

n-3 Long-chain polyunsaturated fatty acids in mood and behaviour

To date, studies have investigated the effects of *n*-3PUFA in relation to various aspects of mood and behaviour. The majority of this work has focused on a role for *n*-3PUFA in the development and treatment of depression and a variety of depressive illnesses, but work is also available on anxiety and anxiety-related disorders, aggression, hostility and anti-social disorders, inattention, impulsivity and attention deficit hyperactivity disorder (ADHD) and other psychiatric symptoms and disorders, such as schizophrenia. The present review will consider each of these in turn. Where studies measure more than one aspect of mood, these studies are included separately in the discussion of each condition. Aspects of cognitive function, such as vigilance, concentration and disorders of cognitive function, such as Alzheimer's' disease, while closely associated with mood and behaviour, are not covered.

Depression, depressive illness and suicidal behaviour

Depression is characterised by high levels of depressed or low mood, a loss of interest or pleasure in nearly all activities, changes in appetite, weight, sleep or activity, decreased energy, difficulties thinking, concentrating or making decisions, feelings of worthlessness or guilt, and recurrent thoughts of death or suicidal ideation, plans or attempts. Depressive disorders are defined by two consecutive weeks of depressed mood or loss of interest in nearly all activities, plus verification of four additional symptoms[33]. Epidemiological, clinical and trial evidence investigating a role for *n*-3PUFA in depression and depressive illness is available.

Epidemiological evidence

Studies investigating the association between the dietary intake of *n*-3PUFA and depression are given in Table 1[34–59]. Four ecological studies have found negative linear and non-linear associations between national fish consumption and national prevalence of major depression[34,39], postpartum depression[36] and bipolar disorders[37]. These studies, however, use crude population (rather than individual) measures of *n*-3PUFA intake and depressive illness, and few potential confounders of *n*-3PUFA intake and depression are considered.

The majority of epidemiological studies investigating *n*-3PUFA intakes and depression have been conducted within individuals. Studies have used FFQ and diet recalls to record fish consumption, seafood consumption and the whole diet, and all studies measured self-reported depression, although different questionnaires have been used. Of the eleven (within-individual) studies reported in Table 1, eight studies found a negative association between fish or *n*-3PUFA intake and depression[41–43,46–48,50,51], although in two studies, associations were only found in female participants[42,47], and in one study associations were found for fish intake but not for fish + *n*-3PUFA supplement intake[50], whereas in another study associations were found for calculated total *n*-3PUFA intake but not for fish intake[46]. Three studies found no associations[44,45,49]. In seven of the studies that found associations, the relationship between *n*-3PUFA intake and depression was found following adjustment for confounders[41–43,46–48,51]. In three of these studies, however, associations were reduced following adjustment for confounders[43,46,51], and in one study no association between *n*-3PUFA intake and depressed mood remained following adjustment for the confounders, age and deprivation[50].

Clinical evidence

Clinical studies typically investigate associations between *n*-3PUFA status and depressive illness, and either compare individuals suffering from depressive symptoms with controls, or investigate the continuous relationship between *n*-3PUFA status and depressive symptom severity. Details of

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Table 1. Epidemiological evidence investigating a role for *n*-3 long-chain PUFA (*n*-3PUFA) in depression and depressed mood

Study	Subjects	*n*-3PUFA intake estimate	Outcome	Findings
Hibbeln (1998)[34]	Eight countries (total *n* 35 000)	Annual fish catch plus imports minus exports	Prevalence of major depression using structural interviews and DSM-III criteria[35]	Negative linear relationship. No adjustment for confounders
Hibbeln (2002)[36]	Twenty-two countries (total *n* 14 532)	Annual fish catch plus imports minus exports	Prevalence of postpartum depression using EPDS cut-offs	Negative non-linear relationship. Relationship remained if countries were omitted as confounders due to low SES or unmarried mothers (*n* 2), or Asian (*n* 4)
Noaghiul & Hibbeln (2003)[37]	Twelve countries	Annual fish catch plus imports minus exports[38]	Prevalence of bipolar disorder I, II and spectrum using structured interviews and DSM-III criteria[35]	Negative non-linear associations for all outcomes. No adjustment for confounders
Peet (2004)[39]	Eight countries	FOASTAT[40] database of apparent national food consumption (total food production plus imports minus exports, changes in stores and food lost in processing)	Prevalence of major depression using structured interviews and DSM-III criteria[34,35]	Negative linear association. No adjustment for confounders
Tanskanen *et al.* (2001)[41]	Finland (*n* 1767)	FFQ question, split as infrequent consumers and frequent consumers of fish (twice per week or more)	Self-report depression (BDI-21 9/10 cut-off), self-reported suicidality (present or absent)	Reduced risk of depression and suicidality in frequent fish consumers compared with infrequent consumers, following adjustment for confounders
Tanskanen *et al.* (2001)[42]	Finland (*n* 3204)	FFQ question, split as infrequent consumers of fish (twice per month or less) and frequent consumers (once per week or more)	Self-report depression (BDI-21 9/10 cut-off)	Negative associations in women. Associations remained following adjustment for confounders. No associations in men
Silvers & Scott (2002)[43]	New Zealand (*n* 4644)	FFQ, split as non-eaters of seafood (none) and eaters of seafood (less than once per month or more)	Self-report mental health (SF-36 mental health scale and mental component scale)	Negative associations. Associations reduced but remained following adjustment for confounding
Hakkarainen *et al.* (2004)[44]	Finland (29 133 men)	Diet history questionnaire of whole diet, split into tertiles of fish and *n*-3PUFA	Self-report depressed mood, hospital treatment due to depressive disorder, death from suicide	No associations
Jacka *et al.* (2004)[45]	Australia (755 women)	FFQ of whole diet, including fish, seafood, *n*-3PUFA supplements, averaged over previous 6 years	Self-report depression based on DSM-IV criteria, split at diagnosis cut-off	No association. No association remained after adjusting for confounders
Suzuki *et al.* (2004)[46]	Japan (771 lung cancer patients)	FFQ of whole diet, split into quartiles of fish and *n*-3PUFA − ALA, OTA, ETA, EPA, DPA, DHA, EPA + DHA, total *n*-3PUFA	Self-report depressed mood (HADS-D cut-off 4/5)	Negative associations with ALA and total *n*-3PUFA. Associations reduced (total *n*-3PUFA) but remained following adjustment for confounders. No association for other *n*-3PUFA or fish/seafood
Timonen *et al.* (2004)[47]	Finland (*n* 5689; 2968 female and 2721 male)	FFQ, split as rare eaters of fish (monthly or less) and regular eaters (weekly or more)	Self-report depression (HSCL-25 2/2·1 cut-off), self-report diagnosed depression, self-report suicidal ideation (HSCL item)	Negative associations for all outcomes in women, following adjustment for confounders. No associations in men
Barberger-Gateau *et al.* (2005)[48]	France (*n* 9294)	FFQ of selected items of diet, split as consumers of fish and seafood < once per week, once per week, > once per week	Self-report depressed mood (CES-D cut-off 16/17 for men, 22/23 for women)	Negative association, following adjustment for confounders
Miyake *et al.* (2006)[49]	Japan (865 women)	Diet history questionnaire of whole diet, split into quartiles of fish, *n*-3PUFA, *n*-6PUFA and *n*-6:*n*-3PUFA	Self-report postpartum depression (EPDS 8/9 cut-off)	No associations. No associations following adjustment for confounders

Table 1. *Continued*

Study	Subjects	*n*-3PUFA intake estimate	Outcome	Findings
Appleton *et al.* (2007)[50]	UK (*n* 2982)	FFQ on intake in last 3 months of white fish, fatty fish and *n*-3PUFA supplements	Self-report depressed mood (DASS-21)	Negative non-linear association for fish. No association following adjustment for confounders. No associations for fish + *n*-3PUFA supplements
Appleton *et al.* (2007)[51]	UK (2747 men); France (7855 men)	FFQ of selected items of diet, including fish	Self-report depressed mood (ten-item questionnaire[52])	Negative non-linear associations. Associations reduced but remained following adjustment for confounders

DSM, Diagnostic and Statistical Manual of Mental Disorders; EPDS, Edinburgh Postnatal Depression Scale[58]; SES, socio-economic status; FOASTAT, Food and Agriculture Organization of the United Nations Statistics; BDI-21, Beck Depression Inventory (twenty-one-item version)[53]; SF-36, MOS Short Form Health Survey[54]; ALA, α-linolenic acid; OTA, octadecatetraenoic acid; ETA, eicosatetraenoic acid; DPA, docosapentaenoic acid; HADS-D, Hospital Anxiety and Depression Scales (depression scale)[55]; HSCL-25, Hopkins Symptom Checklist (twenty-five-item version)[56]; CES-D, Center for Epidemiologic Studies (depression scale)[57]; *n*-6PUFA, *n*-6 long-chain PUFA; DASS-21, Depression, Anxiety and Stress Scales (twenty-one-item version)[59].

studies investigating differences between those with depressive symptoms and those without are given in Table 2[60–83]. The majority of studies have compared individuals with diagnosed clinical depression and controls with no depression, although some studies have also included individuals with undiagnosed, sub-clinical depression[62,66], and some studies have used self-report measure cut-offs to define high levels of depression as opposed to clinical diagnosis[73–76]. Studies on postpartum depression[77,78], suicide attempt[79], bipolar disorder[80,81], self-harm[82] and affective and paranoid disorders[83] are also available. Studies used a variety of different biological samples for assessment of *n*-3PUFA status. The majority of studies involving individuals diagnosed with clinical depression show low levels of a number of *n*-3PUFA and high ratios of *n*-6PUFA:*n*-3PUFA in depressed individuals compared with controls. All studies, however, involve assays of a number of fatty acids, where associations are found for some fatty acids and not others, with no consistent patterns emerging for those comparisons that yield associations or those that do not. Low levels of *n*-6PUFA are also often reported, again in inconsistent patterns, and few studies use adjusted *P* values to take account of multiple testing. Two studies also demonstrate higher levels of *n*-3PUFA in depressed individuals compared with controls[60,61]. Comparisons of individuals with other depressive illnesses reveal some differences between cases and controls, where cases have lower levels of some *n*-3PUFA, but again patterns of associations are inconsistent[79–83]. Comparisons between individuals with high and low levels of undiagnosed depression reveal few differences between groups[73–78].

Studies investigating relationships between *n*-3PUFA status and depressive symptomatology are given in Table 3[53,55,57,58,61,62,64,65,67,73,74,76,77,79,82,84–97]. These studies show similar patterns to those above. Negative associations between depressive symptoms and *n*-3PUFA status, and positive associations between depressive symptoms and *n*-6PUFA:*n*-3PUFA balance have been found, but again patterns with individual *n*-3PUFA are inconsistent and the majority of assays do not find associations.

A few clinical studies have also investigated the association between *n*-3PUFA intake and depressive illness in groups of patients. One study again found negative associations between *n*-3PUFA intake and depression[64], although no association between *n*-3PUFA intake and a number of depressive illnesses and behaviours has also been reported[61,78,79]. These studies, however, are typically small, often fail to account adequately for confounding factors as above, and due to the difficulty of accurately measuring usual diet, are far from conclusive.

Trial evidence

Trials measure the effects of *n*-3PUFA supplementation either compared with placebo (placebo-controlled trials) or with no comparison (open-label trials). A number of open-label trials have investigated the impact of supplementation with *n*-3PUFA on depression. Studies are typically small (between six and thirty-seven participants), and the majority

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Table 2. Clinical evidence investigating a role for *n*-3 long-chain PUFA (*n*-3PUFA) in depression and depressed mood: comparisons between depressed cases and non-depressed controls

Study	Population	Biological sample (% by wt unless otherwise stated)	Comparison	*n*-3	ALA	20 : 3*n*-3	EPA	22 : 3*n*-3	DPA *n*-3	DHA	*n*-6	LA	18 : 3*n*-6	18 : 4*n*-6	20 : 2*n*-6	20 : 3*n*-6	AA	Adrenic acid	DPA *n*-6	*n*-6 : *n*-3	AA : EPA	AA : DHA	DPA *n*-6 : DHA	Other
Ellis & Sanders (1977)[60]	C endogenous depression	PCPG	C *v.* controls				↑		x	↑						x	x							
Fehily *et al.* (1981)[61]	C endogenous depression	PCPG	C *v.* controls				↑		x	↑		↓				x	x							*
		EEPG	C *v.* controls				x		x	↑		x				x	x	x						*
		ECPG	C *v.* controls				x		x	x		↓				x	x	x						*
Maes *et al.* (1996)[62]†	C and SC major depression	PL	C and SC *v.* NC	x	x		x		x	x	x	x	x		x	x	x	x	x	x				*
		PL	C *v.* SC	x	x		x		x	x	x	x	x		x	x	x	x	x	x				*
		CE	C and SC *v.* NC	x	↓		x			x	x	x	x			x	x							*
		CE	C *v.* SC	x	x		x			x	x	x	x			x	x							*
Peet *et al.* (1998)[63]	C major depression	EM	C *v.* controls	↓	x		x		↓	↓	↓	↓				↓	x	x	x	x	x	x		‡
Edwards *et al.* (1998)[64]	C major depression	EM	C *v.* controls	↓	x		↓		↓	↓	x													*
Maes *et al.* (1999)[65]	C major depression	PL, % wt	C *v.* controls	x	x		↓		↓	x	x	x	x		x	x	x	↓	↑	x	↑		↑	‡
		PL, mg/dl	C *v.* controls	↓	↓		↓		↓	↓	↓	↓	x		x	x	↓	↓	x					‡
		CE, % wt	C *v.* controls	↓	↓		↓		x	x	x	x	x		x	x	x			↑	↑			*
		CE, mg/dl	C *v.* controls	↓	↓		↓		x	x	↓	↓	x		↓	x	↓							‡
Tiemeier *et al.* (2003)[66]	C and SC major depression	PL	C *v.* controls	x			x		x	↓	x	x				x	↑			↑	x	↑		*
		PL	C and SC *v.* NC (CES-D cut-off 15/16)	x			x		x	x	x	x				x	x			x	x	x		*
	With CRP < 1·5 mg/l	PL	C *v.* controls	↓			↓		x	↓	x	x				x	x			↑	↑	↑		*
	With CRP > 1·5 mg/l	PL	C *v.* controls	x			x		x	x	x	x				x	x			x	x	x		*
Parker *et al.* (2006)[67]	C major depression in ACS patients	PL, mg/dl	C *v.* controls	x			x			x														
	C major depression in ACS patients (outliers removed)	PL, mg/dl	C *v.* controls	↓			x			↓														
Frasure-Smith *et al.* (2004)[68]	C major depression in ACS patients	PL	C *v.* controls	↓	x		x		x	↓	x	x	↑			x	x	↑	x	↑	↑	↑		*
Schins *et al.* (2007)[69]	C depression in MI patients	PL	C *v.* controls																		↑			
De Vriese *et al.* (2003)[70]	C postpartum	PL	C *v.* controls	↓	x		x			↓	x	x					x			↑	x			
		CE	C *v.* controls	↓	x		x			↓	x	x					x			x	x			
Assies *et al.* (2004)[71]	C major depression	EM, mol*	C *v.* controls		x		x		x	x		x	x		x	x	x	x	x					*
		L	C *v.* controls		x		x		x	x		x	x		x	x	x	x	x					*
McNamara *et al.* (2007)[72]	C major depression	Brain	C *v.* controls							↓							x	x	x					*

Table 2. *Continued*

Study	Population	Biological sample (% by wt unless otherwise stated)	Comparison	*n*-3	ALA	20 : 3*n*-3	EPA	22 : 3*n*-3	DPA *n*-3	DHA	*n*-6	LA	18 : 3*n*-6	18 : 4*n*-6	20 : 2*n*-6	20 : 3*n*-6	AA	Adrenic acid	DPA *n*-6	*n*-6 : *n*-3	AA : EPA	AA : DHA	DPA *n*-6 : DHA	Other
	C major depression	Brain	C Suicide death *v.* C non-suicide death							x							x	x	x					*
Mamalakis *et al.* (2002)[73]	NC depression	AT	NC *v.* SC (ZSDS cut-off 40/41)	x	x		x		x	↓	x	x			x	x	x							
Mamalakis *et al.* (2004)[74]	NC adolescent depression	AT	BDI (cut-off 15/16)	x	x	x	x	x	x	x	x	x	x		x	x	x			x				‡
			CES-D (cut-off 15/16)	x	x	x	x	x	x	x	x	x	x		x	x	x			x				‡
Kobayakawa *et al.* (2005)[75]	NC depression in lung cancer patients	EM	C *v.* SC (HADS-D cut-off 9/10)	↓	x		x		↓	↓										x				
			SC *v.* NC (HADS-D cut-off 4/5)	x	x		x		x	x										x				
			C *v.* NC	x	x		x		x	x										x				
Mamalakis *et al.* (2006)[76]	NC depression	CE	GDS-15 (≤ 5 *v.* > 5)	x	x		x		x	x	x	x	x			x	x			x		x		
		AT		↓	↓	x	x	x	x	x	x	x	x		x	x	x			x		x		
Otto *et al.* (2003)[77]	NC postpartum	PL	EPDS ≥ 10 *v.* EPDS < 10				x									x								
Browne *et al.* (2006)[78]	NC postpartum	L	C *v.* NC	x			x			x										x				
			C and SC *v.* NC (BDI ≥ 10 or EPDS ≥ 9 *v.* BDI < 10 or EPDS < 9)	x			x			x										x				
Huan *et al.* (2004)[79]	NC suicide attempt	EM	Suicide attempt *v.* controls	↓	x		↓		↓	↓	x	x				x	x	x	x	↑				‡
Chiu *et al.* (2003)[80]	C bipolar	EM	C *v.* controls	x	x		x			↓	x	x	x				↓			x	x			
Ranjekar *et al.* (2003)[81]	C bipolar	EM	C *v.* controls		↓		↓			x		x	x				x							*
Garland *et al.* (2007)[82]	C self-harm	L	C *v.* controls	↓	x		↓			↓	↓	↓					x							*
Kaiya *et al.* (1991)[83]	C affective and paranoid disorders	PL, mg/dl	C *v.* controls		x		x		x	x		x				x	x							*
		CE, mg/dl	C *v.* controls		x		x			x		↓	x			x	x							*

ALA, α-linolenic acid; DPA, docosapentaenoic acid; LA, linoleic acid; AA, arachidonic acid; C, clinical; PCPG, plasma choline phosphoacylglycerols; ↑, higher PUFA in depressed cases compared with comparison; x, no association; ↓, lower PUFA in depressed cases compared with comparison; EEPG, erythrocyte ethanolamine phosphoacylglycerols; ECPG, erythrocyte choline phosphoacylglycerols; SC, sub-clinical; PL, plasma phospholipids; NC, non-clinical; CE, plasma cholesteryl esters; EM, erythrocyte membranes; CES-D, Center for Epidemiologic Studies (depression scale)[57]; CRP, C-reactive protein; ACS, acute coronary syndromes; MI, myocardial infarction; mol*, concentration calculated with references to the internal standard 18-methylnonadecanoic acid; L, plasma lipids; AT, adipose tissue; ZSDS, Zung Self-Rating Depression Scale[84]; BDI, Beck Depression Inventory[53]; HADS-D, Hospital Anxiety and Depression Scales (depression scale)[55]; GDS-15, Geriatric Depression Scale (fifteen-item version)[85]; EPDS, Edinburgh Postnatal Depression Scale[58].

* Other *n*-3PUFA tested but no associations found.

† Results following adjustment for multiple testing.

‡ Other *n*-3PUFA tested and associations found.

Table 3. Clinical evidence investigating a role for *n*-3 long-chain PUFA (*n*-3PUFA) in depression and depressed mood: associations between *n*-3PUFA status and depressive symptom severity

Study	Population	Outcome	Scale	Biological sample (% by wt unless otherwise stated)	*n*-3	ALA	20 : 3*n*-3	EPA	22 : 3*n*-3	DPA *n*-3	DHA	*n*-6	LA	18 : 3*n*-6	20 : 2*n*-6	20 : 3*n*-6	AA	22 : 2*n*-6	Adrenic acid	DPA *n*-6	*n*-6 : *n*-3	AA : EPA	AA : DHA	DPA *n*-6 : DHA	Others
Fehily *et al.* (1981)[61]	C only depression	Endogenous depression	BDI	PCPG							+														
		Reactive depression	BDI	PCPG							x														
Maes *et al.* (1996)[62]	C depression	Depression	HDRS	CE	x	x		x			x	x	x	x		x	x								
				PL	x	x		x		x	x	x	x	x	x	x	x		x	x					
Adams *et al.* (1996)[86]	C only major depression	Depression	HDRS	EM				x		x	x										x	+			
		Depression	HDRS	PL, mg/dl				x		x	x										x	x			
		Depression	Linear	EM				−		x	x										+	+			
		Depression	Linear	PL, mg/dl				x		−	x										x	+			
Edwards *et al.* (1998)[64]	C only major depression	Depression	BDI	EM	−	−		x		x	−														
	All	Depression	BDI	EM	x	x		x		x	−		+												
Maes *et al.* (1999)[65]	C only major depression	Depression	HDRS	PL	x	x		x		x	x	x	x	x	x	x	x				x	x			*
	C only major depression	Depression	HDRS	CE	x	x		x		x	x	x	x	x	x	x	x				x	x			*
Parker *et al.* (2006)[67]	C major depression in ACS patients	Depression	DMI-18	PL	x			x			−														
Mamalakis *et al.* (2002)[73]	NC depression	Depression	ZSDS	AT	x	x		x		x	−	x	x		x	−	x								
Mamalakis *et al.* (2004)[74]	NC depression, adolescents	Depression	BDI	AT	x	x	x	x	x	x	x	x	x	x	x	x	x				x				†
		Depression	CES-D	AT	x	x	x	x	x	x	x	x	x	x	x	x	x				x				†
Mamalakis *et al.* (2006)[76]	NC depression	Depression	GDS-15	CE	x	x		x		x	x	x	x	x		x	x				x		+		
		Depression	GDS-15	AT	x	−	x	x	x	x	x	x	x	x	x	x	x				x		x		
Mamalakis *et al.* (2006)[87]	NC depression, adolescents	Depression	BDI	AT		x	x	−‡		x	x		x	x	x	x	x								
		Depression	CES-D	AT		x	x	x		x	x		x	x	x	+[$]	x								
Mamalakis *et al.* (2006)[88]	NC depression	Depression	ZSDS	AT		x	x	x		−	−		x	x	x	x	x	x		x					*
Llorente *et al.* (2003)[89]	NC postpartum	Depression	BDI	PL							x														
Otto *et al.* (2003)[77]	NC postpartum	Depression	EPDS	PL, mg/l							x									x				x	
Kilkens *et al.* (2004)[90]	NC depression in IBS patients and controls	Depression	SCL – depression	PL	x																				
	NC depression in IBS patients and controls (outliers removed)		SCL – depression	PL	−																+	+			
			HADS	PL	x																+	x			
Assies *et al.* (2001)[91]	C schizophrenia	Depression	MADRS	EM, mol*	x	−		x		x	x	x	x	−	x	x	x		x	x	x	x	x		†

Table 3. *Continued*

Study	Population	Outcome	Scale	Biological sample (% by wt unless otherwise stated)	*n*-3	ALA	20 : 3*n*-3	EPA	22 : 3*n*-3	DPA *n*-3	DHA	*n*-6	LA	18 : 3*n*-6	20 : 2*n*-6	20 : 3*n*-6	AA	22 : 2*n*-6	Adrenic acid	DPA *n*-6	*n*-6 : *n*-3	AA : EPA	AA : DHA	DPA *n*-6 : DHA	Others
Huan *et al.* (2004)[79]	Suicide attempt	Depression	HDRS, SIS	EM				x			x														
Garland *et al.* (2007)[82]	C self-harm	Depression	BDI	L	–							–													
Sublette *et al.* (2007)[92]	C major depression	Suicide	No. of attempts	PL				x			–						x				+				

ALA, α-linolenic acid; DPA, docosapentaenoic acid; LA, linoleic acid; AA, arachidonic acid; C, clinical; BDI, Beck Depression Inventory[(53)]; PCPG, plasma choline phosphoacylglycerols; +, positive correlation; x, no correlation; HDRS, Hamilton Depression Rating Scale[(93)]; CE, plasma cholesteryl esters; PL, plasma phospholipids; EM, erythrocyte membranes; –, negative correlation; DMI-18, Depression in the Medically Ill (eighteen-item version)[(94)]; NC, non-clinical; ZSDS, Zung Self-Rating Depression Scale[(84)]; AT, adipose tissue; CES-D, Center for Epidemiologic Studies (depression scale)[(57)]; GDS-15, Geriatric Depression Scale (fifteen-item version)[(95)]; EPDS, Edinburgh Postnatal Depression Scale[(58)]; IBS, irritable bowel syndrome; SCL, Symptom Checklist (ninety-item version)[(96)]; HADS-D, Hospital Anxiety and Depression Scales (depression scale)[(55)]; MADRS, Montgomery–Asberg Depression Rating Scale[(66)]; mol*, concentration calculated with references to the internal standard 18-methylnonadecanoic acid; SIS, Suicide Intent Scale[(97)]; L, plasma lipids.

* Other *n*-3PUFA tested but no associations found.
† Other *n*-3PUFA tested and associations found.
‡ No correlation, but significant negative predictor in regression model.
§ Significant correlation and significant positive predictor in regression model.

of studies have found decreases in depression or depressive symptoms. Freeman *et al.* found decreases in diagnosed major depression[(98)] and diagnosed postpartum depression[(99)] following different doses of EPA + DHA, Osher *et al.* [(100)] found decreases in bipolar depression following supplementation with EPA, and Wozniak *et al.* [(101)] found decreases in diagnosed childhood bipolar depression following supplementation with EPA + DHA. Wozniak *et al.* [(101)] also found decreases in mania and psychotic symptoms following supplementation and Sagduyu *et al.* [(102)] found decreases in mania and bipolar symptoms following supplementation with EPA + DHA. Case reports of treatment with *n*-3PUFA for depressive disorders have also yielded benefits[(103,104)]. Marangell *et al.* [(105)], however, found no benefits of EPA + DHA on depression in a non-clinical sample of women with a history of postpartum depression, and Kaplan *et al.* [(106)] found no benefits of EPA on depression in a sample diagnosed with post-traumatic stress disorder.

Placebo-controlled trials investigating the effects of *n*-3PUFA on depression and depressive symptoms are shown in Table 4[(12,33,53,59,89,93,96,107–137)]. Most studies have involved individuals diagnosed with major depression, but some studies have involved individuals diagnosed with bipolar disorders[(12,114–116)] and some studies have involved volunteers without diagnosis of depression[(89,117–119)] or individuals with other psychiatric conditions[(120–126)]. Of the studies conducted in individuals with diagnosed major depression, two studies found decreases in depression following supplementation with EPA + DHA compared with placebo[(110,112)], two studies found decreases in depression following supplementation with EPA ethyl ester (E-EPA) compared with placebo[(107,108)], although Peet & Horrobin[(108)] only found benefits for 1 g E-EPA, and not for 2 g E-EPA or 4 g E-EPA, and three studies found no differences between treatment and placebo groups following supplementation with DHA[(109)] or EPA + DHA[(111,113)]. Of the studies involving individuals with bipolar disorder, two studies found decreases in depression and in bipolar symptoms following supplementation with EPA + DHA compared with placebo[(114)] or E-EPA compared with placebo[(115)], although neither study found similar improvements in mania. Two studies, however, found no benefit of supplementation with EPA + DHA[(12)] or E-EPA[(116)] for depression, mania or bipolar symptoms. All four studies involving volunteers with no diagnosis of depression also found no differences between treatment and placebo groups following supplementation with DHA[(89)], EPA + DHA[(119)], EPA + DHA + other *n*-3PUFA[(118)] or advice to eat fish or supplementation with EPA[(117)]. Of the studies involving individuals with other psychiatric conditions, one study found a beneficial effect of EPA + DHA compared with placebo on depression in chronic fatigue patients[(120)], one study found a beneficial effect of E-EPA compared with placebo on depression in patients with borderline personality disorder[(124)] and one study found a benefit of EPA + DHA compared with placebo on depression in individuals who self-harm[(126)]. Hallahan *et al.* [(126)] also found a beneficial effect of EPA + DHA supplementation on the presence or absence of suicidal ideation. However, one study also found no improvement in depression

https://doi.org/10.1017/S0954422408998620 Published online by Cambridge University Press

Table 4. Trial evidence investigating a role for *n*-3 long-chain PUFA (*n*-3PUFA) in depression and depressed mood: placebo-controlled trials

Authors	Participant group	Sample *n*: total (treatment/placebo)	Daily dose	Duration (d)	Outcome	Outcome measure	Findings
Nemets *et al.* (2002)[107]	C unipolar depressive disorder	20 (10/10)	2·0 g E-EPA	28	Depression	HDRS	Significant decrease in depression in treatment *v.* control
Peet & Horrobin (2002)[108]	C major depression	70 (17 at 1 g per d, 18 at 2 g per d, 17 at 4 g per d/18)	1, 2 or 4 g E-EPA	84	Depression	HDRS, MADRS, BDI	Significant decreases in depression from 1 g *v.* placebo. No significant differences between 2 g or 4 g and placebo. Significant improvements over time
Marangell *et al.* (2003)[109]	C major depression	36 (18/18)	2·0 g DHA	42	Depression	MADRS, HDRS, GAF	No significant differences between groups
Su *et al.* (2003)[110]	C major depression	28 (14/14)	4·4 g EPA +2·2 g DHA	56	Depression	HDRS	Significant decrease in depression in treatment *v.* placebo
Silvers *et al.* (2005)[111]	C major depression	77 (40/37)	0·6 g EPA +2·4 g DHA	84	Depression	HDRS-SF, BDI	No significant differences between groups. Significant decreases over time
Nemets *et al.* (2006)[112]	C major depression (childhood 6–12 years)	28 (13/15)	0·38–0·4 g EPA +0·18–0·2 g DHA	112	Depression	CDRS, CDI, CGI	Significant decreases in depression in treatment *v.* placebo in all measures. Significant decreases over time
Grenyer *et al.* (2007)[113]	C major depression	83 (40/43)	0·6 g EPA +2·2 g DHA	112	Depression	HDRS, BDI	No significant differences between groups. Significant effects of time
					Personal functioning	GAF	No significant differences between groups. Significant effects of time
Stoll *et al.* (1999)[114]	C bipolar disorder (I or II)	30 (14/16)	6·2 g EPA +3·4 g DHA	112	Depression	HDRS	Significant decrease in depression in treatment *v.* control
					Mania	YMRS	No significant differences between groups. Significant improvements over time
					Bipolar symptoms	CGI, GAF	Significant improvement in symptoms in both measures in treatment *v.* control
Hirashima *et al.* (2004)[12]	C bipolar disorder (I)	21 (12/9)	5·0–5·2 g EPA +3·0–3·4 g DHA or 1·3 g EPA +0·7 g DHA	28	Depression	HDRS	No significant differences between groups
					Mania	YMRS	No significant differences between groups
Frangou *et al.* (2006)[115]	C bipolar disorder (I or II)	75 (24 at 1 g per d, 25 at 2 g per d/26)	1 or 2 g E-EPA	84	Depression	HDRS	Significant decreases in depression in 1 g and 2 g treatment *v.* placebo
					Mania	YMRS	No significant differences between groups
					Bipolar symptoms	CGI, no. needing adjustment to medication	Significant decreases in symptoms in 1 g and 2 g treatment *v.* placebo. Seven patients in 1 g and 2 g treatment groups *v.* twelve patients in placebo
Keck *et al.* (2006)[116]	C bipolar disorder (I, II or NOS)	116 (59/57)	6·0 g E-EPA	120	Depression	IDS-C	No significant differences between groups

Table 4. *Continued*

Authors	Participant group	Sample *n*: total (treatment/placebo)	Daily dose	Duration (d)	Outcome	Outcome measure	Findings
					Mania	YMRS	No significant differences between groups
					Bipolar symptoms	CGI-BP	No significant differences between groups
Llorente *et al.* (2003)[89]	NC postpartum depression	99 (44/45)	Approximately 0·2 g DHA	120	Depression	BDI, EPDS, SCID-CV	No significant differences between groups
Ness *et al.* (2003)[117]	Angina sufferers	452 (229/223)	Fish (or EPA)*	180	Depression	DSP – depression	No significant differences between groups
Fontani *et al.* (2005)[118]	NC healthy volunteers	33 (33/33) (w-s cross-over design)	1·6 g EPA + 0·8 g DHA + 0·4 g other *n*-3 fatty acids	35	Depression	POMS – depression	No significant differences between groups
Rogers *et al.* (2008)[119]	NC depressed mood	218 (109/109)	0·63 g EPA + 0·85 g DHA	84	Depression	DASS – depression	No significant differences between groups
Behan *et al.* (1990)[120]	C chronic fatigue syndrome	63 (39/24)	0·14 g EPA + 0·09 g DHA	90	Depression	Four-point Likert scale	Significant decreases in treatment *v.* control
Warren *et al.* (1999)[121]	C chronic fatigue syndrome	50 (24/26)	0·14 g EPA + 0·09 g DHA	90	Depression	BDI	No significant differences between groups
Fenton *et al.* (2001)[122]	C schizophrenia	87 (43/44)	3·0 g E-EPA	112	Depression	MADRS	No significant differences between groups. Significant effects of time
Peet & Horrobin (2002)[123]	C schizophrenia	122 (29/28/27/31)	1 g, 2 g or 4 g E-EPA	84	Depression	MADRS	No significant differences between groups
Zanarini & Frankenburg (2003)[124]	C borderline personality disorder	30 (20/10)	1·0 g E-EPA	56	Depression	MADRS	Significant decrease in treatment *v.* placebo. Significant effects of time
Fux *et al.* (2004)[125]	C obsessive–compulsive disorder	11 (11/11) (w-s cross-over design)	2·0 g E-EPA	42	Depression	HDRS	No significant differences between groups
Hallahan *et al.* (2007)[126]	C self-harm (16 years plus)	49 (22/27)	1220 mg EPA + 908 mg DHA	84	Depression	BDI, HDRS	Significant decreases in treatment *v.* placebo in both measures
					Suicidal ideation	Presence or absence (MOAS subscale)	Significant reduction in treatment *v.* placebo

C, clinical; E-EPA, ethyl ester EPA; HDRS, Hamilton Depression Rating Scale[93]; MADRS, Montgomery–Asberg Depression Rating Scale[96]; BDI, Beck Depression Inventory[53]; GAF, Global Assessment of Functioning[33]; HDRS-SF, Hamilton Depression Rating Scale, short form[127]; CDRS, Children's Depression Rating Scale[128]; CDI, Children's Depression Inventory[129]; CGI, Clinical Global Impression[130]; YMRS, Young Mania Rating Scale[131]; NOS, not otherwise specified; IDS-C, Inventory of Depressive Symptomology[132]; CGI-BP, Clinical Global Impression – bipolar disorder[133]; NC, non-clinical; EPDS, Edinburgh Postnatal Depression Scale[58]; SCID-CV, Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV axis I disorders – clinical version[134]; DSP, Derogatis Stress Profile[135]; w-s, within-subjects; POMS, Profile of Mood States (depression question)[136]; DASS, Depression, Anxiety and Stress Scales (depression scale)[59]; MOAS, Modified Overt Aggression Scale[137].
*Advised to eat more fatty fish (mackerel, herring, kipper, pilchard, sardine, salmon, trout) or given EPA capsules; recommended dose is not reported.

following EPA + DHA supplementation in chronic fatigue patients[121], one study found no improvement in depression following supplementation with E-EPA in patients with obsessive–compulsive disorder[125] and two studies found no improvements in depression following E-EPA supplementation in schizophrenic patients[122,123].

Evaluation

Evidence of a role for *n*-3PUFA in depressive disorders is inconclusive. Epidemiological studies provide some evidence that *n*-3PUFA intake is associated with depressed mood, but not all studies have found associations, and some studies have found effects that have subsequently disappeared on consideration of confounders. Clinical studies also provide some evidence that depression may be associated with reduced *n*-3PUFA status, although the results are inconclusive. With some exceptions, the majority of studies are small, conducted on highly selected samples, and studies that find no associations between *n*-3PUFA or reverse associations are also available.

Evidence on the effects of *n*-3PUFA supplementation on depression is also inconclusive. Greatest evidence for a beneficial effect of supplementation with *n*-3PUFA can be found in the studies involving individuals diagnosed with major depression, but even here studies finding no benefit are also available. Evidence from individuals with bipolar disorders and other psychiatric conditions is equivocal. Evidence from the three trials involving individuals with non-diagnosed depression suggests no benefit of *n*-3PUFA supplementation on depression in these individuals.

Four recent meta-analyses have attempted to evaluate the evidence from placebo-controlled trials investigating a role for *n*-3PUFA in depression[138–141]. Differences between analyses exist dependent on inclusion criteria, but all four suggest a beneficial effect of *n*-3PUFA for depressive illness – combined effect sizes range from 0·13 (95 % CI 0·01, 0·25) to 0·61 (95 % CI 0·21, 1·01). All four meta-analyses also report clear heterogeneity between study findings, and the three conducted following a systematic review of the published literature[138,140,141] also suggest considerable publication bias, where small studies reporting positive findings are more likely to be published than small studies showing negative findings[138]. The heterogeneity and publication bias in these analyses argue for caution when interpreting the overall effect sizes. The combined effect size and heterogeneity from the most recent meta-analysis conducted[141] are clearly demonstrated in the relevant Forest plot (see Fig. 2). A beneficial effect of *n*-3PUFA compared with placebo was also found by Lin & Su[140] when combining trials investigating a role for *n*-3PUFA in bipolar disorder (combined effect size 0·69 (95 % CI 0·28, 1·10), although heterogeneity and publication bias were also found. However, no differences between treatment and placebo were found by Appleton *et al.* [138] when combining trials investigating a role for *n*-3PUFA in individuals with no diagnosis of depressive disorder (combined standardised mean difference −0·13 (95 % CI −0·29, 0·02) SD).

Anxiety

Anxiety is defined as a state of uneasiness or tension caused by apprehension of possible misfortune or danger[142]. Anxiety disorders include panic attacks, phobias, specific anxiety disorders, obsessive–compulsive disorder and generalised anxiety disorder. All are characterised by an intense or persistent apprehension, worry, fearfulness or terror[33].

Epidemiological evidence

No studies of which we are aware have investigated the association between *n*-3PUFA intake and anxiety or anxiety-related conditions.

Clinical evidence

One study has investigated associations between anxiety and *n*-3PUFA status[143]. Individuals clinically diagnosed with social anxiety disorder were found to have lower levels of *n*-3PUFA, higher levels of *n*-6PUFA and higher ratios of *n*-6PUFA:*n*-3PUFA than controls. Severity of anxiety symptoms was also negatively correlated with *n*-3PUFA levels and positively correlated with *n*-6PUFA levels.

Trial evidence

Five studies have investigated the effects of *n*-3PUFA supplementation on anxiety and anxiety-related conditions. Ness *et al.* [117] measured anxiety following advice to eat fish or supplementation with EPA in a large sample (*n* 452) of angina sufferers, Fontani *et al.* [118] measured anxiety following supplementation with EPA + DHA + other *n*-3PUFA in thirty-three healthy volunteers, Rogers *et al.* [119] measured anxiety following supplementation with EPA + DHA in 218 individuals with mild–moderate depressed mood, Fux *et al.* [125] studied anxiety and obsessive–compulsive behaviour following E-EPA in eleven individuals diagnosed with obsessive–compulsive disorder, and Yehuda *et al.* [144] studied mood and organisational abilities following supplementation with ALA in a group of 126 test anxiety sufferers. Improvements following treatment compared with placebo were found in two studies[118,144], but no benefits of treatment compared with placebo were found in the other three studies[117,119,125].

Evaluation

Evidence investigating a role for *n*-3PUFA in anxiety and anxiety related conditions is very limited and, at present, equivocal. One clinical and two supplementation studies suggest that *n*-3PUFA may be implicated in anxiety, three supplementation studies suggest no role for *n*-3PUFA in anxiety. Further research is clearly required, however, before clear judgements can be made.

Fatigue

Fatigue is defined as a physical or mental exhaustion due to exertion[142] and is a key component of several behavioural

https://doi.org/10.1017/S0954422408998620 Published online by Cambridge University Press

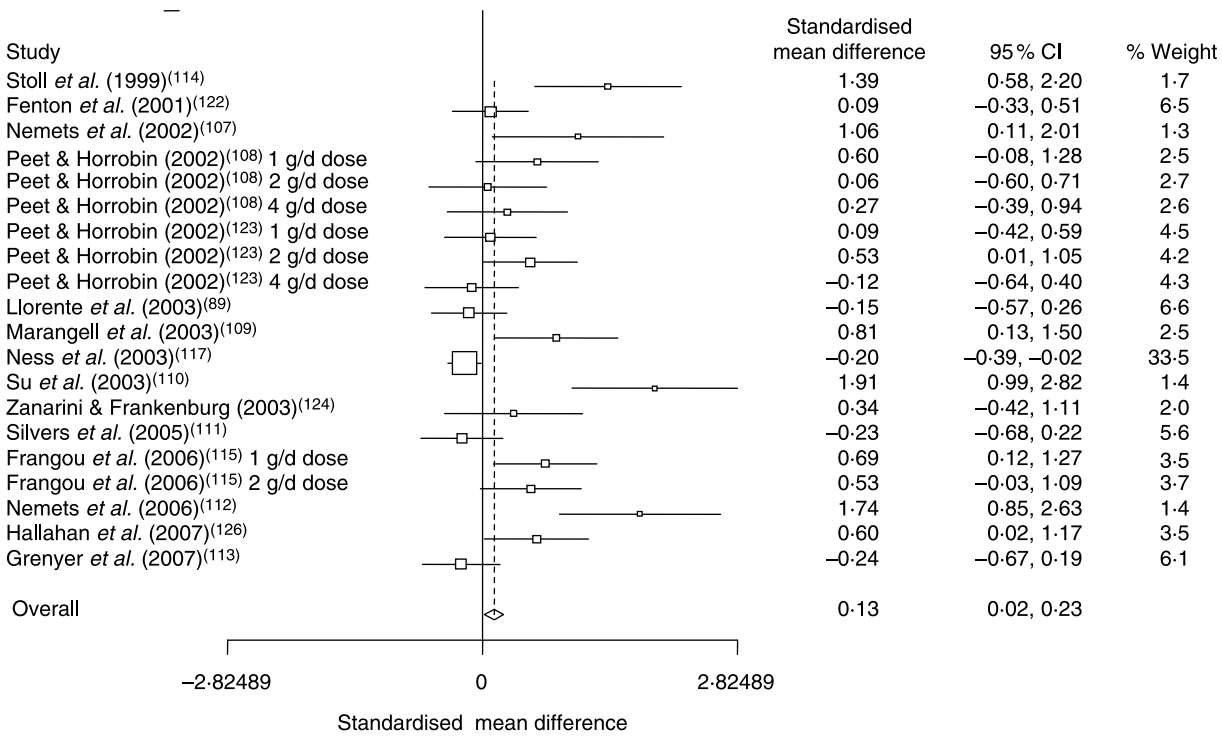

Fig. 2. Forest plot for the meta-analysis of all randomised controlled trials investigating the effects of *n*-3 long-chain PUFA on depressed mood up to September 2007 (taken from Appleton *et al.*[141]).

conditions such as chronic fatigue syndrome and post-viral fatigue syndrome[145].

Epidemiological evidence

No studies of which we are aware have investigated the association between *n*-3PUFA intake and fatigue or fatigue-related conditions.

Clinical evidence

Three studies of which we are aware have investigated associations between *n*-3PUFA status and fatigue. Two of these studies found no differences between individuals diagnosed with chronic fatigue and controls in *n*-3PUFA status[120,121], although differences in *n*-6PUFA and saturated fats were found in one study[120]. The third study[146] found elevated DHA levels and higher ratios of *n*-6PUFA:*n*-3PUFA in chronic fatigue patients, and found positive associations between *n*-6PUFA:*n*-3PUFA balance and fatigue symptoms. This study, however, also found associations between fatigue symptoms and levels of *n*-6PUFA.

Trial evidence

Five studies have included measurement of fatigue following *n*-3PUFA supplementation compared with placebo[113,118,120,121,144]. Of these studies, Behan *et al.*[120] found decreases in fatigue following supplementation with EPA + DHA compared with placebo in sixty-three individuals diagnosed with chronic fatigue syndrome, Fontani *et al.*[118] found decreases following supplementation with EPA + DHA compared with placebo in thirty-three healthy volunteers, and Yehuda *et al.*[144] found decreases in fatigue following supplementation with ALA + *n*-6PUFA compared with placebo in 126 individuals suffering from test anxiety. Benefits of *n*-3PUFA supplementation for individuals with chronic fatigue syndrome have also been reported in several individual cases[147]. However, no differences between treatment and placebo groups were found by Warren *et al.*[121] using a supplement of EPA + DHA + *n*-6PUFA in fifty individuals, or by Grenyer *et al.*[113] using a supplement of EPA + DHA in eighty-three individuals.

Evaluation

Evidence investigating a role for *n*-3PUFA in fatigue and related conditions is very limited and, at present, equivocal. One clinical and three supplementation studies suggest that *n*-3PUFA may be implicated in fatigue; however, two clinical studies and two supplementation studies also suggest no role for *n*-3PUFA in the development or treatment of fatigue. Further research is clearly required, however, before clear judgements can be made.

Aggression, hostility and anti-social behaviour

Aggression is defined as 'a hostile or destructive mental attitude or behaviour'[142], hostility is defined as 'enmity or antagonism'[142], and at extremes, both aggressive and hostile behaviours can result in a diagnosis of one of a

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number of impulsive control disorders, such as intermittent explosive disorder. Impulse control disorders are characterised by 'the failure to resist an impulse drive or temptation to perform an act that is harmful to the individual or to others'[33]. For the majority of disorders, the individual feels an increasing sense of tension or arousal before committing an aggressive act, experiences pleasure, gratification or relief at the time of committing the act, and then may or may not feel regret, self-reproach or guilt[33].

Epidemiological evidence

Epidemiological investigation of associations between *n*-3PUFA intake and hostility have been undertaken in one study, using diet histories and self-report hostility measured using the Cook–Medley Hostility Scale[148] in 3581 young adults[149]. This study found negative associations between hostility and DHA content of the diet and consumption of fish rich in *n*-3PUFA. No associations, however, were found between hostility and other *n*-3PUFA, *n*-6PUFA:*n*-3PUFA balance or consumption of all fish.

Clinical studies

Three studies of which we are aware have investigated *n*-3PUFA status in relation to aggressive or violent behaviour. One of these studies found lower levels of *n*-3PUFA and DHA, and almost higher *n*-6PUFA:*n*-3PUFA balance in aggressive compared with non-aggressive cocaine dependants[150]. The other two studies, however, found no differences between violent and non-violent controls or between individuals diagnosed with intermittent explosive disorder and controls in *n*-3PUFA status[151,152]. Virkkunen *et al.* [152] did find lower levels of DHA in individuals diagnosed with personality disorder compared with controls, but greater differences were found in levels of *n*-6PUFA, which were markedly higher in patients than controls.

Trial evidence

One open-label study investigated the effects of *n*-3PUFA supplementation on irritability in thirty-four patients suffering from bipolar disorder, and found benefits[102]. A further open-label study, however, investigated the effects of *n*-3PUFA supplementation on anger and hostility in individuals suffering from post-traumatic stress disorder and found no effects[106].

Placebo-controlled trials investigating the effects of *n*-3PUFA on aggression, anger, hostility, tension, irritability and anti-social behaviour are given in Table 5[118,119,124,126,136,137,148,153–166]. Of the twelve studies reported, two studies found decreases in aggression following supplementation with E-EPA[124], or EPA + DHA compared with placebo[155], one study found decreases in anger following supplementation with EPA + DHA + other *n*-3PUFA compared with placebo[118], one study found decreases in tension following supplementation with EPA + DHA + other *n*-3PUFA compared with placebo[159], and one study found decreases in anti-social behaviour following supplementation with EPA + DHA + *n*-6PUFA + vitamins + minerals compared with placebo[160]. Two further studies also found improvements in aggression following supplementation compared with placebo, where aggression increased in the placebo group but remained stable in the group treated with EPA + DHA[153,156]. Four of the studies report no differences in aggression/irritability between treatment and placebo groups following supplementation[126,155,157,158], one study reports no differences in hostility between treatment and placebo groups[154] and one study reports no differences in anger between treatment and placebo groups[119]. One study also reports increases in aggression following supplementation with EPA + DHA compared with placebo[156], and one study reports decreases in aggression following placebo compared with treatment following supplementation with EPA + DHA[154].

Evaluation

Evidence of the effects of *n*-3PUFA on aggression and hostility is again equivocal. Epidemiological evidence suggests relationships between some aspects of *n*-3PUFA intake and aggression or hostility, but not others. Some clinical studies have found associations whereas others have not. Trial studies also provide equivocal evidence of a benefit from and an absence of effects of *n*-3PUFA supplementation on aggression or hostility. Authors in this area have suggested that the absence of clear effects may be due to an effect of *n*-3PUFA which is only demonstrated in stressful situations or individuals under stress[155], and that *n*-3PUFA may be beneficial in protecting against an increase in aggression in vulnerable situations or in individuals predisposed to aggressive or violent behaviour.

Inattention, hyperactivity, impulsivity and attention deficit hyperactivity disorder

Inattention is defined as not paying attention, hyperactivity is defined as abnormal activity and impulsivity is defined by actions based on sudden desires, whims or inclinations, rather than careful thought[142]. ADHD is characterised by a persistent pattern of inattention and hyperactivity–impulsivity that is more frequent and severe than is typically observed in individuals at a comparable level of development. For formal diagnosis, some hyperactivity–impulsivity symptoms that cause impairments must have been present before the age of 7 years, some impairment from symptoms must be present in at least two settings, and clear evidence of developmentally inappropriate social, academic and occupational functioning must exist[33]. Symptoms of inattention and/or hyperactivity–impulsivity of insufficient severity to warrant formal diagnosis also occur[33].

Epidemiological evidence

Only one study of which we are aware has used epidemiological evidence to investigate the association between *n*-3PUFA intake and inattention, impulsivity or ADHD, although this study used maternal *n*-3PUFA intake during pregnancy, and measures of inattention, hyperactivity and behavioural disorders in offspring[167]. The study found increased seafood consumption during pregnancy was associated with decreased behavioural problems; however,

https://doi.org/10.1017/S0954422408998620 Published online by Cambridge University Press

Table 5. Trial evidence investigating a role for *n*-3 long-chain PUFA (*n*-3PUFA) in aggression, hostility and anti-social behaviour: placebo-controlled trials

Authors	Participant group	Sample *n*: total (treatment/ placebo), followed by number in analysis if different	Daily dose	Duration (d)	Outcome	Outcome measure	Findings
Hamazaki *et al.* (1996)[153]	NC young adults	53 (27/26) 41 (22/19)	1·5–1·8 g DHA + 0·2–0·25 g EPA	90	Extra-aggression*	P-F Study	Significant increases in aggression in placebo *v.* treatment
Hamazaki *et al.* (1998)[154]	NC young adults	59 (29/30)	1·5 g DHA + 0·2 g EPA	91	Extra-aggression*	P-F Study	Significant decreases in aggression in placebo *v.* treatment
					Hostility	Cook–Medley Hostility Scale[148]	No significant differences between groups
Hamazaki *et al.* (2002)[155]	NC elderly white-collar workers (*n* 21) and villagers (*n* 19)	41 (20/21) 40 (19/21)	0·2 g EPA + 1·5 g DHA	60	Extra-aggression*	PF Study	Significant decreases in treatment *v.* placebo in white-collar workers (*n* 21). No significant differences between groups in villagers (*n* 19)
Itomura *et al.* (2005)[156]	NC children 9–12 years	179 (89/90) 166 (83/83)	3·6 g DHA + 0·84 g EPA/week, provided in foods	90	Physical aggression	HAQ-C	Significant increases in physical aggression in placebo *v.* treatment in females
					Extra-aggression*	P-F Study	Significant increases in extra-aggression in treatment *v.* placebo in all participants
Fontani *et al.* (2005)[118]	NC healthy volunteers	33 (33/33) (w-s cross-over design)	1·6 g EPA + 0·8 g DHA + 0·4 g other *n*-3 fatty acids	35	Anger	POMS – anger	Significant decreases in anger in treatment *v.* placebo
Rogers *et al.* (2008)[119]	NC depressed mood	218 (109/109)	0·63 g EPA + 0·85 g DHA	84	Anger	STAXI – anger	No significant differences between groups
Hirayama *et al.* (2004)[157]	C childhood ADHD 6–12 years	40 (20/20)	3·6 g DHA + 0·7 g EPA/week, provided in foods	60	Aggression	Two questions to parents and teachers	No significant differences between groups
Amminger *et al.* (2007)[158]	C childhood and adolescent autism (7–13 years)	13 (7/6) 12 (7/5)	840 mg EPA + 700 mg DHA	42	Irritability	ABC	No significant differences between groups
Hallahan *et al.* (2007)[126]	C self-harm (16 years plus)	49 (22/27)	1·2 g EPA + 0·9 g DHA	84	Aggression, irritability	MOAS	No significant differences between groups
Zanarini & Frankenburg (2003)[124]	C borderline personality disorder	30 (20/10)	1·0 g E-EPA	56	Aggression	MOAS	Significant decrease in treatment *v.* placebo
Buydens-Branchey & Branchey (2006)[159]	C substance abusers	24 (13/11)	2·25 g EPA + 0·5 g DHA + 0·25 g other *n*-3PUFA	90	Tension	POMS – tension	Significant decrease in tension in treatment *v.* placebo
Gesch *et al.* (2002)[160]	NC prisoners	231 (116/115)	80 mg EPA + 44 mg DHA + *n*-6PUFA + vitamins and minerals	Self-selected (mean 142)	Anti-social behaviour	No. of offences	Significant decreases in treatment *v.* placebo

NC, non-clinical; P-F Study, Picture Frustration Study[161,162]; HAQ-C, Hostility–Aggression Questionnaire for Children[163,164]; w-s, within-subjects; POMS, Profile of Mood States (anger question, tension question)[136]; STAXI, State-Trait Anger Expression Inventory[165]; C, clinical; ADHD, attention deficit hyperactivity disorder; ABC, Aberrant Behaviour Checklist[166]; MOAS, Modified Overt Aggression Scale[137]; E-EPA, ethyl ester EPA; *n*-6PUFA, *n*-6 long-chain PUFA.
* Extra-aggression is outward aggression towards other people or objects.

only associations with prosocial behaviour and social development remained after adjustment for confounders.

Clinical evidence

Several studies have investigated the associations between *n*-3PUFA status and inattention, hyperactivity and impulsivity[168–172]. Four of these studies found low levels of *n*-3PUFA in individuals with ADHD symptoms compared with controls[169–172], and all studies found low levels of DHA in these individuals. Two studies also found high ratios of *n*-6PUFA:*n*-3PUFA in those with ADHD symptoms compared with controls[169,172]. Four studies found low levels of *n*-6PUFA in those with symptoms[168–170,172]. Stevens *et al.* [169] also found a continuous association between DHA levels and ADHD symptom severity as measured by parents, but no associations were found based on teacher ratings, and similar associations were not found by Young *et al.* [171] using self-report questionnaires. Investigating behavioural symptoms in children with high and low *n*-3PUFA status, Stevens *et al.* [173] also found associations between low *n*-3PUFA status and high parental ratings of hyperactivity, impulsivity and conduct disorders, although no associations were found in teachers' ratings. Conversely, Stevens *et al.* [170] also found higher levels of *n*-3PUFA and lower *n*-6PUFA: *n*-3PUFA balance in individuals with ADHD symptoms compared with controls, using measurements from erythrocytes as opposed to plasma lipids.

Antalis *et al.* [172] and Stevens *et al.* [169] also studied *n*-3PUFA intake in young adults diagnosed with ADHD compared with controls. Antalis *et al.* [172] found no differences in intakes of *n*-3PUFA or *n*-6PUFA in cases and controls, although Stevens *et al.* [169] found higher intakes of PUFA in cases than in controls.

Trial evidence

One open-label study investigated the effects of supplementation with ALA and vitamins on inattention, hyperactivity and impulsivity in thirty children diagnosed with ADHD, and found reductions in all three measures[174]. One further open-label study investigated the effects of *n*-3PUFA supplementation on impulsivity in individuals suffering from post-traumatic stress disorder, but this study found no effects[106].

Nine studies of which we are aware have investigated the effects of *n*-3PUFA on inattention, impulsivity and related conditions, as given in Table 6[126,156–158,166,170,175–186]. The majority of studies have been conducted on children diagnosed with ADHD[157,170,175,176], but studies are also available involving children with no clinical mood diagnoses[156,177], children diagnosed with developmental co-ordination disorder[178], children and adolescents diagnosed with autism[158] and adults with diagnosed self-harm[126]. Three studies found improvements in inattention following supplementation with EPA + DHA + *n*-6PUFA[170,177,178] compared with placebo, two studies found improvements in hyperactivity following supplementation with EPA + DHA[158] and EPA + DHA + *n*-6PUFA[178] compared with placebo, one study found improvements in impulsivity following supplementation with EPA + DHA[156], two studies found improvements in general ADHD symptoms following supplementation with EPA + DHA + *n*-6PUFA[177,178] compared with placebo, and one study found improvements in disruptive behaviour following supplementation with EPA + DHA + *n*-6PUFA[170]. The majority of these studies, however, measured inattention, hyperactivity, impulsivity and conduct as described by parents and teachers, but found effects only in selected measures. Three studies also found no benefits of *n*-3PUFA compared with placebo for inattention, hyperactivity or impulsivity[157,175] or impulsivity alone[126], and one study found no benefits of *n*-3PUFA compared with current medication (Ritalin)[176].

Evaluation

The one epidemiological study provides no evidence of a role for *n*-3PUFA in inattention, hyperactivity and impulsivity, once confounders are taken into consideration. The findings from clinical studies suggest that *n*-3PUFA and particularly DHA may be important in inattention, impulsive and disruptive behaviours, although evidence is currently very limited. The findings from trials are currently equivocal, and the evidence overall is far from conclusive. The majority of studies have found benefits from *n*-3PUFA supplementation on selected aspects of mood or behaviour, although no benefits are found for other aspects of mood or behaviour, and studies that fail to find effects are also available.

Schizophrenic disorders

Schizophrenia is defined by a mixture of characteristic (positive and negative) signs and symptoms which have been present for a significant proportion of time during a 1-month period with indications of the disorder persisting for at least 6 months. Positive symptoms reflect an extension or distortion of normal functions, for example, delusions, hallucinations, and disorganised speech or behaviour. Negative symptoms reflect a diminution or loss of normal functions, for example, restrictions in the range or intensity of emotional expression, restrictions in the fluency or productivity of thought or speech, and restrictions in the initiation of goal-directed behaviour[33]. Epidemiological, clinical and trial evidence investigating a role for *n*-3PUFA in schizophrenia and schizophrenic disorders is available.

Epidemiological evidence

Three studies have investigated associations between *n*-3PUFA intake and schizophrenia. One ecological study investigated the association between total fat, fat from animals and birds and fat from fish and vegetables in the diet and course and outcome of schizophrenia in eight countries. This study found a positive association between poorer course and outcome for schizophrenia and total fat consumption and consumption of fat from animals and birds, and no association between schizophrenia course or outcome and fat from fish and vegetables, although in a regression model both a high consumption of fat from animals and birds and a low consumption of fat from fish

https://doi.org/10.1017/S0954422408998620 Published online by Cambridge University Press

Table 6. Trial evidence investigating a role for *n*-3 long-chain PUFA (*n*-3PUFA) in inattention, hyperactivity, impulsivity and attention deficit hyperactivity disorder: placebo-controlled trials

Authors	Participant group	Sample *n*: total (treatment/ placebo), followed by number in analysis if different	Daily dose	Duration (d)	Outcome	Outcome measure	Findings
Voigt *et al.* (2001)[175]	C childhood ADHD (7–11 years)	63 (32/31) 54 (27/27)	345 mg DHA	120	Inattention	TOVA, CCT	No significant differences between groups. Significant effects of time
					Impulsivity	TOVA	No significant differences between groups. Significant effects of time
					ADHD symptoms	CBC, CPRS	No significant differences between groups.
Harding *et al.* (2003)[176]	C childhood ADHD (7–12 years)	20 (10/10)	180 mg EPA + 120 mg DHA + *n*-6PUFA + vitamins and minerals (comparison – Ritalin)	28	Impulsivity	IVA/CPT – FSRCQ	No significant differences between groups. Significant differences over time
					Inattentiveness	IVA/CPT – FSACQ	No significant differences between groups. Significant differences over time
Stevens *et al.* (2003)[170]	C childhood ADHD with thirst or skin symptoms of EFA deficiency (6–13 years)	50 (25/25) 47 (25/22)	480 mg DHA + 80 mg EPA + 136 mg *n*-6PUFA	120	Attention deficit, hyperactivity	Parent and Teacher CASQ, Parent and Teacher DBD – hyperactivity, DBD – attention	Significant decreases in inattention (teachers) in treatment *v.* placebo. Significant effects of time
					Disruptive behaviour	Parent and Teacher DBD – conduct, DBD – defiant disorder	Significant decreases in conduct (parents) in treatment *v.* placebo. Significant effects of time
Hirayama *et al.* (2004)[157]	C childhood ADHD (6–12 years)	40 (20/20)	3·6 g DHA + 0·7 g EPA/week, provided in foods	60	Inattention, hyperactivity, impulsivity	ADHD diagnostic criteria, rated by parents and teachers, Impulsivity test	No significant differences between groups
Richardson & Puri (2002)[177]	NC children (8–12 years)	41 (22/19) 29 (15/14)	186 mg EPA + 480 mg DHA + *n*-6PUFA	84	ADHD symptoms	CPRS-L	Significant decreases in total scores and inattention in treatment *v.* placebo. Significant decreases over time
Itomura *et al.* (2005)[156]	NC children (9–12 years)	166 (83/83)	3·6 g DHA + 0·84 g EPA/week	90	Inattention, hyperactivity, impulsivity	ADHD diagnostic criteria	Significant decreases in impulsivity in females in treatment *v.* placebo
Richardson & Montgomery (2005)[178]	C childhood developmental co-ordination disorder (5–12 years)	117 (60/57)	558 mg EPA + 174 mg DHA + 60 mg *n*-6PUFA	90	ADHD symptoms	CPRS-L	Significant decreases in total scores, inattention and hyperactivity in treatment *v.* placebo
Amminger *et al.* (2007)[158]	C childhood and adolescent autism (7–13 years)	13 (7/6)	840 mg EPA + 700 mg DHA	42	Hyperactivity	ABC – hyperactivity	Significant decreases in treatment *v.* placebo
Hallahan *et al.* (2007)[126]	C self-harm (16 years plus)	49 (22/27)	1220 mg EPA + 908 mg DHA	84	Impulsivity	IMT/DMT	No significant differences between groups

C, clinical; ADHD, attention deficit hyperactivity disorder; TOVA, Test of Variables of Attention[179]; CCT, Children's Color Trials Test[180]; CBC, Child Behaviour Checklist[181]; CPRS, Conners' Parent Rating Scales[182]; IVA/CPT – FSRCQ, Intermediate Visual and Auditory/Continuous Performance Test – Full Scale Response Control Quotient[183]; IVA/CPT – FSACQ, Intermediate Visual and Auditory/Continuous Performance Test – Full Scale Attention Control Quotient[183]; EFA, essential fatty acid; *n*-6PUFA, *n*-6 long-chain PUFA; CASQ, Conners' Abbreviated Symptom Questionnaires[184]; DBD, Disruptive Behaviour Disorders Rating Scale[185]; NC, non-clinical; CPRS-L, Conners' Parent Rating Scales (long version)[182]; ABC, Aberrant Behaviour Checklist[166]; IMT/DMT, Immediate and Delayed Memory Tasks[186].

and vegetables were predictive of poorer schizophrenia outcome[187]. A second ecological study conducted on data from fourteen countries found no association between seafood consumption and prevalence rates of schizophrenia[37]. One study in the USA investigated the relationship between the whole diet and a clinical diagnosis of schizophrenia in 146 schizophrenic patients compared with population norms. This study also found positive associations between schizophrenia and consumption of saturated fat and polyunsaturated fats, but no association with *n*-3PUFA[188].

Clinical evidence

Associations between *n*-3PUFA status and schizophrenia or schizophrenic symptoms, assessed by comparison of individuals with schizophrenia compared with controls, are shown in Table 7[81,83,91,189–201]. Patterns in *n*-3PUFA status are again inconclusive. Ten studies show decreased levels of *n*-3PUFA in schizophrenics compared with controls, while four studies show elevated levels of *n*-3PUFA in schizophrenics compared with controls[83,189,190–198]. Two studies show increases in *n*-6PUFA:*n*-3PUFA (arachidonic acid: DHA) ratios in schizophrenics compared with controls[91,201] and two studies show decreases in *n*-6PUFA:*n*-3PUFA ratios[190,198]. All studies except five[91,189,195–197] also found decreased *n*-6PUFA in schizophrenics compared with controls.

Studies that investigate relationships between levels of *n*-3PUFA and severity of symptoms show similar inconsistencies. Assies *et al.*[91] found negative associations between EPA status and schizophrenic symptoms, Reddy *et al.*[199] found no associations between *n*-3PUFA levels and schizophrenic symptoms, Mellor *et al.*[202] found no associations between *n*-3PUFA levels and schizophrenic symptoms, and positive associations with involuntary movement, but Peet *et al.*[198] found positive associations between DHA status and positive schizophrenic symptoms, and Richardson *et al.*[203] found positive associations between *n*-3PUFA levels and positive schizotypal trait measures in healthy adults, and no associations with negative schizotypal trait measures. Three studies also found positive associations between *n*-6PUFA levels and schizophrenic symptoms[91,202] or schizotypal trait measures[203], although Peet *et al.*[198] found negative associations between linoleic acid status and negative schizophrenic symptoms.

Trial evidence

Several open-label studies have investigated the effects of *n*-3PUFA on schizophrenic symptoms. These studies found improvements in schizophrenic symptoms following supplementation with EPA[202,204] and improvements in schizophrenic symptoms and quality of life following supplementation with EPA + DHA[196]. Case reports of treatment with *n*-3PUFA for schizophrenia have also yielded benefits[205,206].

Five placebo-controlled studies of which we are aware have investigated the effects of supplementation with *n*-3PUFA on schizophrenic symptoms. Peet *et al.*[207] found decreases in symptoms following EPA supplementation at 2 g/d for 3 months compared with placebo in two studies, and Emsley *et al.*[208] found decreases in symptoms following E-EPA supplementation at 2 g/d compared with placebo for 12 weeks. Peet & Horrobin[123] also found decreases in symptoms following supplementation with 2 g E-EPA/d compared with placebo for 12 weeks in patients with adjunctive treatment with clozapine, although limited effects were found for 1 g/d and 4 g/d doses and in patients with other adjunctive medication, and no effects of any dose or in any group were found on involuntary movement. Fenton *et al.*[122] also found no improvements in schizophrenic symptoms or in involuntary movement following supplementation with 3 g E-EPA/d compared with placebo for 16 weeks and Peet *et al.*[207] found no effects on schizophrenic symptoms from supplementation with 2 g DHA/d compared with placebo for 3 months.

Evaluation

Epidemiological evidence suggests that *n*-3PUFA intakes may be unimportant in schizophrenia and schizophrenic conditions, although total PUFA or total fat intake may be important. Clinical studies also suggest that schizophrenia may not be associated with biochemical concentrations of *n*-3PUFA, but that levels of total PUFA or total fat may be more important. Studies of *n*-3PUFA supplementation have found some benefits of *n*-3PUFA for schizophrenia, although the results of one meta-analysis, to date, suggest no benefits of *n*-3PUFA supplementation compared with placebo (combined mean difference of −2·61 (95 % CI −6·37, 1·15) Positive and Negative Syndrome Scale scores[139]. Only very limited evidence, however, is clearly currently available.

Other mood and behavioural disorders

In investigation of other mood or behavioural disorders, a potential role for *n*-3PUFA has also been suggested in autism and Asperger's syndrome. Autism is defined by the presence of markedly abnormal or impaired development in social interaction and communication, and a markedly restricted repertoire of activity and interests[33]. Asperger's syndrome is defined by severe and sustained impairments in social interaction and the development of restricted and repetitive patterns of behaviour, interests and activities[33].

In support of an association between *n*-3PUFA and autism and/or Asperger's syndrome, Vancassel *et al.*[209] found low levels of *n*-3PUFA and higher ratios of *n*-6PUFA:*n*-3PUFA in individuals with autism compared with mentally retarded individuals, Bell *et al.*[210] found lower levels of *n*-3PUFA, and particularly docosapentaenoic acid *n*-3 in individuals with autism and individuals with Asperger's syndrome compared with controls, and Johnson & Hollander[211] found beneficial effects of supplementation with EPA in one individual with autism. However, in a placebo-controlled trial conducted in thirteen children and adolescents with diagnosed autism, no benefit of EPA + DHA was found[158]. Evidence in this area is clearly too limited to draw reliable conclusions.

https://doi.org/10.1017/S0954422408998620 Published online by Cambridge University Press

Table 7. Clinical evidence investigating a role for *n*-3 long-chain PUFA (*n*-3PUFA) in schizophrenia: comparisons between cases and controls

Study	Population	Biological sample	Comparison	*n*-3	ALA	18 : 4*n*-3	20 : 3*n*-3	EPA	22 : 3*n*-3	DPA *n*-3	DHA	*n*-6	LA	18 : 3*n*-6	18 : 4*n*-6	20 : 2*n*-6	20 : 3*n*-6	AA	22 : 2*n*-6	Adrenic acid	DPA *n*-6	*n*-6 : *n*-3	AA : EPA	AA : DHA	DPA *n*-6 : DHA	Other
Obi & Nwanze (1979)[189]	C schizophrenia	PL	C0 *v.* controls		↑																					*
			C24 *v.* controls		↑																					*
		EM	C0 *v.* controls		↑																					*
			C24 *v.* controls		↑																					*
Horrobin *et al.* (1989)[190]	C schizophrenia	PL	C *v.* controls (Scotland)	x	↑			x		x	x	↓	↓				↓	↓		x	↑	↓				*
			C *v.* controls (Ireland)	x				x		x	↑	↓	↓				x	x		x		↓				*
			C with TD *v.* controls (England)	↑	↑			x		x	↑	↓	↓				↓	↓		x	x	↓				†
			C without TD *v.* controls (England)	↑	↑			x		x	x	↓	↓				↓	x		x	x	↓				†
Kaiya *et al.* (1991)[83]	C schizophrenia	PL	C *v.* controls		x			x		↑	x		↓					x		x						*
		CE	C *v.* controls		x			x			x		↓	x			x	x								†
Yao *et al.* (1994)[191]	C schizophrenia	EM, mol/ml	Treated C *v.* controls							x	x		x			x	x	x		x						*
		EM, %wt	Treated C *v.* controls							x	x		↓			x	x	↓		x						†
		EM, mol/ml	Drug-free C *v.* controls							x	x		x			x	x	x		x						*
		EM, %wt	Drug-free C *v.* controls							x	x		↓			x	x	↓		x						†
Peet *et al.* (1995)[192]	C schizophrenia	EM	C *v.* controls		x			↓		x	↓		↓				x	↓	x	x						†
Yao *et al.* (2000)[193]	C schizophrenia	Brain	C *v.* controls with mental disorders							x	x		x			x		↓		x						†
			C *v.* controls without mental disorders							x	x		↓			x		↓		x						†
Assies *et al.* (2001)[91]	C schizophrenia	EM	C *v.* controls	↓	x			x		↓	↓	x	x	x		↑	x	x		x	x	x	x	↑		†
Khan *et al.* (2002)[194]	C schizophrenia	EM	First-episode C *v.* controls							↓	↓		↓					↓								†
			Chronic C *v.* controls							↓	↓		↓					↓								†
Landen *et al.* (2002)[195]	C schizophrenia	Brain	C *v.* controls	x						x	x	x				x	x	x		x	x					*
Arvindashan *et al.* (2003)[196]	C schizophrenia	EM	C *v.* controls					↓			↓		x					↑								†
Evans *et al.* (2003)[197]	C schizophrenia	EM	C0 *v.* controls							↓	↓		x					x								*
			C24 *v.* controls							x	x		x					x								†
Ranjekar *et al.* (2003)[81]	C schizophrenia	EM	C *v.* controls	↓	↓			↓			↓	↓						x								*
Peet *et al.* (2004)[198]	C Indian schizophrenia	EM	C *v.* controls	x							↑	x	↓					x		↓		↓				
	C Malaysian schizophrenia	EM	C *v.* controls	↑				x		↓	↑	x	x				↓	x		↓		↓				
Reddy *et al.* (2004)[199]	C schizophrenia and schizoaffective disorder	EM	C *v.* controls							↓	↓		x	x				↓								
Kemperman *et al.* (2006)[200]	C schizophrenia	EM	C *v.* controls	↓	↓			x		x	↓	↓	x			↓	↑	↓		↓	↓	x			x	†

Table 7. *Continued*

Study	Population	Biological sample	Comparison	*n*-3	ALA	18 : 4*n*-3	20 : 3*n*-3	EPA	22 : 3*n*-3	DPA *n*-3	DHA	*n*-6	LA	18 : 3*n*-6	18 : 4*n*-6	20 : 2*n*-6	20 : 3*n*-6	AA	22 : 2*n*-6	Adrenic acid	DPA *n*-6	*n*-6 : *n*-3	AA : EPA	AA : DHA	DPA *n*-6 : DHA	Other
McNamara *et al.* (2007)[201]	C schizophrenia	Brain	C *v.* controls								↓							×		×	×			↑	×	†
			C (CV death) *v.* controls (CV death)								↓							↓								†
			C (suicide) *v.* controls (CV death)								×							×								*

ALA, α-linolenic acid; DPA, docosapentaenoic acid; LA, linoleic acid; AA, arachidonic acid; C, clinical; PL, plasma phospholipids; C0, untreated clinical population; ↑, higher PUFA in cases compared with comparison; C24, clinical population treated for 24 weeks; EM, erythrocyte membranes; x, no association; ↓, lower PUFA in cases compared with comparison; TD, Tardive dyskinesia; CE, plasma cholesteryl esters; CV, cardiovascular.

* Other *n*-3PUFA tested but no associations found.

† Other *n*-3PUFA tested and associations found.

n-3 Long-chain polyunsaturated fatty acids in mood and behaviour – evaluation

Evidence available investigating a role for *n*-3PUFA in mood and behaviour is highly inconsistent. The greatest available evidence investigates a role for *n*-3PUFA in depression and depressive disorders, but this evidence provides no clear picture of the role of *n*-3PUFA in these conditions. Evidence suggesting a role for *n*-3PUFA in anxiety and fatigue is much more limited but equally equivocal. Evidence suggesting a role for *n*-3PUFA in aggression, anger and hostility is also equivocal. Studies investigating a role for *n*-3PUFA in inattention, hyperactivity, impulsivity and ADHD do suggest some associations, although evidence is far from conclusive. Studies investigating schizophrenia and schizophrenic disorders suggest no clear role for *n*-3PUFA in these conditions, but evidence again is far from conclusive.

While findings are inconsistent, so too is the methodology used to attain these findings. Evidence is provided from epidemiological and clinical studies and from trials. Large epidemiological studies have the advantage of investigation of the population as a whole, but their cross-sectional and observational nature, and their lack of precision and detail severely limit the conclusions that can be drawn from them. While associations between *n*-3PUFA intake and various aspects of mood and mood disorders may be found, a direct association is far from necessary, and a causal association, even less so. All associations are bidirectional or may be explained by some third party. Behavioural evidence suggests various mood disorders to be associated with subsequent decreases in self-care and healthful behaviours, such as consumption of a healthy diet[212]. Behavioural and lifestyle variables have also been associated both with mood disorders and with dietary intake, and may explain any relationship between the two[48,50,51]. The attenuation of relationships between *n*-3PUFA intake and depression following adjustment for confounding variables suggests that any association between *n*-3PUFA intake and depression is unlikely to be a genuine association[50,51], and similar explanations may also apply for other aspects of mood or behaviour. Adequate consideration and measurement of potential confounders, however, can be difficult.

Epidemiological evidence is also based on fish or *n*-3PUFA intakes. Because of the essential nature of *n*-3PUFA, dietary intakes of *n*-3PUFA can be suggested to closely reflect *n*-3PUFA status[78]. However, fish intake may not be a good proxy for *n*-3PUFA status as it is dependent on the type of fish consumed, and plant sources of *n*-3PUFA, such as nuts and seeds, rely on biological conversion to longer-chain *n*-3PUFA before affecting longer-chain *n*-3PUFA function and status[213]. *n*-3PUFA intake may also not be a good proxy for *n*-3PUFA status, as *n*-3PUFA status depends on *n*-3PUFA metabolism and synthesis as well as *n*-3PUFA intake, and the relationship between intake and incorporation into tissues has been found to be non-linear[78].

Clinical studies are also disadvantaged by their cross-sectional and observational nature, again limiting the

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conclusions that can be drawn. Clinical studies that find an association between biological status and mood are often used to suggest a biologically mediated effect on mood; yet, again, causal explanations cannot be drawn from cross-sectional studies such as these. Again, relationships are bidirectional or may be explained by a third party. Evidence suggesting that mood affects *n*-3PUFA status is available from various animal and human studies. Stress is intricately linked with many psychiatric conditions, and 3 weeks of physical and psychological stress has been found to result in decreased neuronal phospholipids and increased lipid peroxidation products in rats[214]. Isolation stress has also been found to result in decreased activity of the Δ5 and Δ6 desaturase enzymes in rats[215], and Brenner[216] reports reductions in the activity of Δ5 and Δ6 desaturase enzymes from a variety of stress-related hormones including adrenalin, adrenocorticotropic hormone, cortisol and steroids in humans. The Δ5 and Δ6 desaturase enzymes are necessary for *n*-3PUFA elongation and synthesis. Smoking and alcohol consumption, often also associated with psychiatric conditions, have also been found to impact on *n*-3PUFA synthesis resulting in reductions in levels[217,218]. Traditional medications for a number of psychiatric conditions may also impact on *n*-3PUFA status, although work on first-episode schizophrenics suggests that medications are unlikely to explain low levels of *n*-3PUFA in these individuals[194,199].

Evidence suggesting that both *n*-3PUFA status and mood may be explained by a third party is also available. Several nutrients that play a role in the metabolism of *n*-3PUFA have also been implicated in the regulation of mood. Erythrocyte concentrations of folate in humans have been associated with mania[219] and plasma concentrations of homocysteine have been associated with hostility, anger[220] and schizophrenia[200], but folate-deficient diets in rats have also been found to result in decreases in DHA in rat plasma[221] and nervous tissue[222]. Mg and Zn deficiency have been reported in children diagnosed with ADHD compared with controls[223,224], Zn deficiency has been correlated with severity of ADHD symptoms[225] and Mg and Zn supplementation has been found to improve ADHD symptoms in children[224,226], but Mg and Zn deficiencies have also been found to result in decreased synthesis of *n*-3PUFA, via reduced activity of desaturase enzymes[227,228]. Hormones and other biological factors may also affect both *n*-3PUFA status and mood[229,230]. Factors related to *n*-3PUFA intake may also affect both *n*-3PUFA status and mood[50].

Clinical studies do offer the precision and detail that cannot be obtained in large epidemiological studies, although they suffer as well, as a result of this precision. The majority of clinical studies are small and conducted on highly selected samples, making confounding factors difficult to adequately control for, and generalisation difficult[231]. Consensus between studies is also difficult due to the use of different biological samples used to measure *n*-3PUFA status. Studies use assays of plasma, erythrocyte membranes, adipose tissue and brain tissue, each thought to be of different potential relevance to mood-related biochemical processes[72].

Well-conducted blinded, placebo-controlled trials can allow investigation of causal explanations. Trial methodology investigating the effects of *n*-3PUFA on mood, however, is also inconsistent. Of possibly greatest potential impact, trials are inconsistent in their use of *n*-3PUFA. Some studies use ALA, some use EPA, some use DHA and others use a combination, yet the suggested potential mechanisms of action of ALA, EPA and DHA on mood differ greatly. Doses of *n*-3PUFA also vary greatly between studies, yet the bioavailability of *n*-3PUFA may differ dependent on source[232], and PUFA synthesis is affected by PUFA levels, so large intakes of *n*-3PUFA may inhibit *n*-3PUFA synthesis[213,233]. Use of *n*-3PUFA alone, or in conjunction with vitamin E, *n*-6PUFA, other vitamins and minerals and existing medications also varies greatly between studies, yet interactions between these compounds are rarely considered[5]. Vitamin E, *n*-6PUFA and various vitamins and minerals may also affect mood, and can impact on *n*-3PUFA synthesis and activity[200,219,220,223–226,234,235].

Second, aspects of mood investigated have been very varied. However, the biochemistry underlying depression, for example, may be very different to the biochemistry underlying anxiety or aggression. Similarly, DHA deficiency is thought to contribute predominantly to the development of postpartum depression[98,99], yet DHA supplementation has not been the focus of study for other forms of depression. Differences between and within trials also exist in their definitions and measurement of outcome mood.

Trials also differ markedly in population studied. Some studies use males, some use females and some use both, yet various hormones impact on *n*-3PUFA synthesis and degradation, and effects may differ in males and females[72,230]. Some studies use adults and others use children, yet *n*-3PUFA metabolism may change with age[229]. Some studies use individuals of low *n*-3PUFA status before the start of the study whereas other do not, yet there is a suggestion that effects of *n*-3PUFA may be found only in deficient individuals[231]. Some studies use clinical populations, some use non-clinical populations; again, effects may differ. A recent series of meta-analyses, for example, found evidence of a beneficial effect of *n*-3PUFA supplementation in individuals with a diagnosed depressive disorder, but found no evidence of a benefit in populations without a depressive diagnosis[138].

Trials also differ in conduct and quality. Trials using poor-quality *n*-3PUFA preparations and a likely fishy aftertaste can be criticised for poor blinding and the possibility of results due to expectations[236]. Trials using olive oil as a placebo have also been criticised due to the potential mood-altering affects of oleamide, a product of oleic acid, a significant component of olive oil[237]. Trials using short time intervals can also be criticised due to the time interval required for *n*-3PUFA to be fully incorporated into the biological system[231].

Differences in methodology currently, however, cannot systematically explain differences in trial outcomes. The benefits of *n*-3PUFA supplementation in some trials provide some evidence that *n*-3PUFA may be implicated in the regulation of mood and behaviour. It is thus possible that *n*-3PUFA do have a role in the regulation of mood and behaviour, but whether that role is direct or indirect is yet to be uncovered.

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The absence of effects in all trials, however, also suggests that implication of *n*-3PUFA in the regulation of mood and behaviour in all individuals seems unlikely, and present theories of a role for *n*-3PUFA in mood and behaviour fail to explain why supplementation with *n*-3PUFA does not benefit all individuals with the same conditions. Individual differences in *n*-3PUFA metabolism, however, have recently been suggested and associated with disruptions to mood and behaviour. Covault *et al.* [238] have found polymorphisms within the gene encoding long-chain fatty acid-CoA ligase type 4 (FACL4), an enzyme important in the incorporation of PUFA into the cell membrane, and found certain polymorphisms to be associated with depression. Pae *et al.* [239] have found polymorphisms in the gene encoding type IV cytosolic phospholipase A_2 (cPLA$_2$) – an enzyme important for *n*-3PUFA uptake, and found certain polymorphisms to be associated with depression. Brookes *et al.* [233] found associations between one of the genes involved in fatty acid synthesis (fatty acid desaturase 2) and clinical diagnosis of ADHD. Schizophrenia has also been associated with one of the genes responsible for the activity of PLA$_2$, a group of enzymes responsible for the incorporation of PUFA into the cell membrane and the degradation of PUFA to form eicosanoids[207]. Alterations in *n*-3PUFA synthesis thus may suggest that certain individuals have a predisposition to disruptions to mood or behaviour. Thus, alterations at different stages of *n*-3PUFA synthesis and degradation may explain why some individuals are affected by some *n*-3PUFA, as opposed to others. Alterations in PUFA synthesis may also explain why supplementation with *n*-3PUFA fails to affect mood in some individuals, dependent on the mechanisms by which *n*-3PUFA affect mood. It has also been argued that, due to the essential nature of PUFA, a predisposition to disruptions to mood or behaviour may be only exposed under certain environmental conditions[240]. Genetic explanations for mood and behaviour, however, fail to explain the recent and continuing increase in mood disorders throughout the world[241].

A role for *n*-3PUFA in the regulation of mood and behaviour is currently far from clear. Furthermore, due to the multi-factorial nature of mood and behaviour, it may be unlikely that any single mechanism is likely to affect or benefit all aspects of mood in all individuals. More work investigating the role of *n*-3PUFA in the regulation of mood and behaviour is clearly required. The greatest need, however, is for more work based on biochemical mechanisms. A role for *n*-3PUFA in various neurotransmitter systems and their links with mood and behaviour need to be clearly elucidated. Similarly, a role for *n*-3PUFA in inflammatory processes and the impact of these on mood and behaviour need to be clearly established. Until the biochemical mechanisms underlying the regulation of different aspects of mood and behaviour are more clearly understood, trials will continue to be designed and explained on an *ad hoc* basis and differences between trials will remain unexplained. Very limited work currently investigates the mechanisms by which mood is regulated in humans, and the means by which *n*-3PUFA may exert effects on these mechanisms. Exact *n*-3PUFA and dose of *n*-3PUFA for supplementation, for example, ought to be based on proposed mechanisms of action. Traditional medications for various psychiatric conditions were developed based on chance findings, with little understanding of underlying mechanisms, and despite success for about 30–60 % of patients treated, little subsequent progress in development has been achieved[242]. We need to ensure a similar pattern of events does not occur for *n*-3PUFA.

A natural remedy for various mood and behavioural conditions, such as *n*-3PUFA, with few side effects and other potential health benefits (for example, for CVD, immune function and inflammatory conditions[2,243]) is highly attractive, yet expense, false hope and limited success in all individuals[244] caution against a blanket recommendation for the use of *n*-3PUFA for mood or behaviour. Side effects following supplementation with *n*-3PUFA have also been reported. Gastrointestinal complaints and loose stools are common[114,245], *n*-3PUFA may adversely affect blood coagulation in individuals treated with anti-coagulants and glucose metabolism in diabetics[245], and Kinrys[246] and Marangell *et al.* [247] report episodes of hypomania following supplementation with *n*-3PUFA. Until more evidence is available, *n*-3PUFA cannot be advocated for the treatment of numerous mood and behavioural conditions.

Conclusion

In conclusion, the evidence currently available from epidemiological, clinical and intervention studies investigating the role of *n*-3PUFA in the regulation of mood and behaviour is limited and highly inconsistent. The field is further compromised by an inadequate understanding of the biochemical mechanisms underlying the regulation of mood and behaviour in humans. There is a clear need for increased high-quality work focusing on understanding the potential mechanisms by which *n*-3PUFA may impact on mood and behaviour. Work appears most advanced (from publications) in relation to schizophrenia[19,248], but further work is needed here as well as in relation to other conditions. An important priority for future research is to conduct adequately powered, well-designed randomised controlled intervention trials, but this should be done in tandem with work investigating the mechanisms by which *n*-3PUFA may affect mood and behaviour.

Acknowledgements

K. M. A. undertook the majority of the research required for and the majority of the writing of this article; P. J. R. and A. R. N. helped with the writing. The work was supported by Queen's University of Belfast (Belfast, UK) and The University of Bristol (Bristol, UK). All authors declare that they have no conflicts of interest.

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