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Essential fatty acids and mood: A systematic review of observational studies

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ABSTRACT

Objective: Essential polyunsaturated (omega-3 and omega-6) fatty acids have been proposed to play a role in the aetiology of mood disorders. However, a systematic review of observational studies has not yet been conducted. Therefore, our aim was to conduct a systematic review of the studies which have investigated the relationship between essential fatty acids and mood in the past 15 years. *Methods:* Four databases (EMBASE, MEDLINE, PsycINFO and ISI Web of Science) were searched for human observational studies of the relationship between essential fatty acids and mood that were published between 1995 and 2009. *Results:* The search yielded a total of 77 papers which met the inclusion criteria. Many of the studies were small, and the methods heterogeneous. Of the studies which investigated dietary fish intake and mood, 75% found a benefit. While 69% of the dietary intake studies observed an inverse relationship between mood and n-3 intake, 82% of the studies which investigated n-3 biomarker status and mood supported a significant inverse association between these two factors. *Conclusions:* The findings of the present review suggest that omega-3 fatty acids are potentially beneficial in enhancing mood and reducing the symptoms of mood disorders (including major depression and bipolar disorder), however the heterogeneity with respect to the methodologies employed by studies in the area renders it difficult to draw absolute conclusions. Further longitudinal studies are warranted in order to determine causality. Dietary fish intake appears to be beneficial in terms of enhancing mood.

Keywords: essential fatty acids, diet, mood, depression, systematic review

INTRODUCTION

Lifetime prevalence rates indicate that approximately 20% of the population are at risk for developing a mood disorder (Kessler, Berglund, Demler, Jin, Merikangas, & Walters, 2005). Numerous dietary factors have been purported to play a part in the pathogenesis of major depression and other mood disorders (Bodnar & Wisner, 2005; Harbottle & Schonfelder, 2008). Over the past 15 years, there has been great interest in the role of omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acids (PUFA) in the aetiology of depression and neuropsychiatric disorders (Young & Conquer, 2005). The parent substrates from which n-3 and n-6 PUFA are derived (alpha-linolenic acid, ALA; and linoleic acid, LA; respectively) are essential fatty acids, as they can be derived only from the diet (Rees, Austin, & Parker, 2005; Sontrop & Campbell, 2006). This is of concern with regard to the typical Western dietary pattern (Oddy, Robinson, Ambrosini, O'Sullivan, de Klerk, Beilin *et al*., 2009), which is low in n-3 PUFA from oily fish and seafood. The typical Western diet comprises a 20-25-fold higher ratio of n-6 to n-3 PUFA, as many processed foods contain n-6 PUFA (Simopoulos, 1999). However, humans evolved on a diet which consisted of an approximately equivalent amount of n-3 and n-6, which may have implications in terms of the pathophysiology of numerous diseases, including depression (Simopoulos, 2002).

A number of potential biochemical mechanisms have been proposed to explain the relationship between essential fatty acid status and mood disorders. One such mechanism involves the observation that n-3 fatty acids have anti-inflammatory properties. This is relevant in the context of observations that overactive immune system mediated inflammation is associated with mood disorders, including bipolar disorder and depression (Young & Conquer, 2005). Other possible mechanisms involve the action of fatty acids on neurotransmitters that have been implicated in the aetiology of mood disorders, namely serotonin and dopamine. Animal studies have demonstrated that a

decrease in dietary n-3 docosahexaenoic acid (DHA) and n-6 arachidonic acid (AA) relates to decreased cortical serotonin and dopamine (Young & Conquer, 2005). Essential fatty acids have also been implicated as regulators of gene transcription within the central nervous system (CNS; Alessandri, Guesnet, Vancassel, Astorg, Denis, Langelier *et al*., 2004). In addition, the ratio of n-3 to n-6 PUFA may play a role in determining neural membrane fluidity, ion channel functioning and receptor binding (Owen, Rees, & Parker, 2008; Stahl, Begg, Weisinger, & Sinclair, 2008).

While a number of studies in the literature suggest that dietary PUFA intake and PUFA status measured via various physiological biomarkers can influence mood, the findings remain equivocal. Various supplementation trials have supported a role for n-3 PUFA as an effective treatment for mood disorders, however the evidence regarding the influence of n-3 PUFA in regulating mood and affect in the general population is inconsistent (Appleton, Rogers, & Ness, 2008). Four systematic reviews have recently investigated the efficacy of n-3 PUFA as a therapeutic treatment for mood disorders (Appleton, Hayward, Gunnell, Peters, Rogers, Kessler *et al*., 2006; Williams, Katz, Ali, Girard, Goodman, & Bell, 2006; Montgomery & Richardson, 2008; Turnbull, Cullen-Drill, & Smaldone, 2008), however observational studies have not yet been subjected to the same scrutiny. Supplementation studies are conducted over a short time-frame, so the potential benefits of long-term n-3 PUFA exposure cannot be reliably determined from such investigations. In addition, supplementation studies are typically conducted in individuals with existing mood disorders. Therefore, it is difficult to determine conclusively whether higher long-term dietary intake of fatty acids, or a higher status of various fatty acids measured via a range of biomarkers, can enhance mood in the 'population at large'. On this basis, we aimed to indentify the observational studies which have addressed this question in the period 1995-2009. In ascertaining the characteristics of all studies published during this period (i.e. sample sizes, age range, study design participant group, exposures and outcomes), the present review is well placed to identify the outcomes between studies which have used different designs to consider the relationship between essential fatty acids and mood.

METHOD

Searches of the online databases EMBASE, MEDLINE, PsycINFO and ISI Web of Science conducted during October 2009 identified articles published between 1995 and the latest update.

Search Terms: The following terms were used to search for papers involving essential fatty acids: essential fatty acid, n-3, omega-3, n-6, omega-6, fish oil, docosahexaenoic, eicosapentaenoic, linolenic, linoleic, arachidonic. These terms were combined with the following terms to capture those studies which investigated mood as an outcome variable: depress$ (truncated term), mood. Searches were limited to human studies published in the English language that were classified as articles, letters (comprising empirical data) or conference proceedings (i.e. reviews, conference abstracts and editorials were not included).

Inclusion and exclusion criteria: Studies were required to investigate the relationship between essential fatty acid exposure and mood. Those which reported essential fatty acid levels on the basis of self-reported dietary intake or via the collection of biomarkers were accepted. In addition, ecological studies that determined fatty acid intake on the basis of national fish consumption were included, as were those that measured mood via self-reported questionnaires, medical diagnosis/clinical interview, admission to a psychiatric ward for treatment of a mood disorder, antidepressant prescription, attempted suicide and/or successful suicide. Ecological studies which measured depression on the basis of national mood disorder prevalence rates were also accepted. Only peer-reviewed, published research articles that employed an observational methodology (i.e. cohort, case-control, cross-sectional and ecological studies) were included. Randomized controlled trials, clinical controlled trials and other study methodologies were not included.

RESULTS

The number of hits returned for each database using our search strategy, in addition to the number which met the inclusion criteria, is reported in Table 1. Further, the number meeting the inclusion criteria for each year between 1995 and 2009, for each of the four databases, is displayed in Figure 1. After removing those articles which appeared in multiple databases, a total of 77 observational (i.e. case-control, cross-sectional, ecological and cohort) studies were included in the systematic review, of which 65 (84%) were published between 2003 and 2009. These were separated into four categories:

- 27 reported the relationship between of *dietary* fatty acid and/or fish intake and mood (see Supplementary Table 1);
- 39 reported the relationship between fatty acid *biomarkers* and mood (see Supplementary Table 2);
- 7 investigated the relationship between fatty acids (measured via dietary intake or biomarkers) and *suicidality or self-harm* (see Supplementary Table 3); and
- 9 investigated the relationship between fatty acids (measured via dietary intake or biomarkers) and *perinatal depression* (see Supplementary Table 4).

Some of the studies met the criteria for two of the categories described above, and were therefore included in both categories for which they fulfilled the criteria.

Dietary Studies: Of the 27 studies which investigated the relationship between dietary fatty acid or fish/seafood intake and mood, two employed a case-control design, 15 were cross-sectional, three were ecological and seven used a cohort design. Eleven were conducted in countries with a relatively large (>30 kg per person, per annum) national seafood intake (Van Vorhees & Prichard, 2009), including Finland (four studies), Japan (three), France (two), Spain and Norway. Six (22%) reported no significant associations (Hakkarainen, Partonen, Haukka, Virtamo, Albanes, & Lonnqvist, 2004; Jacka, Pasco, Henry, Kotowicz, Nicholson, & Berk, 2004; Heath & Berman, 2008; Murakami, Mizoue, Sasaki, Ohta, Sato, Matsushita *et al*., 2008; Oishi, Doi, & Kawakami, 2009; Schiepers, de Groot, Jolles, & van Boxtel, 2009). One further cohort study found no significant linear associations between n-3 PUFA intake or fish intake and depression, but did observe that individuals who reported higher fish intake at baseline and increased their fish intake in the subsequent two years were at a significantly enhanced risk of developing a mental disorder (Sanchez-Villegas, Henriquez, Figueiras, Ortuno, Lahortiga, & Martinez-Gonzalez, 2007). An additional investigation, which employed a cohort design, reported a positive relationship between depression and total (n-3 + n-6) PUFA (Kyrozis, Psaltopoulou, Stathopoulos, Trichopoulos, Vassilopoulos, & Trichopoulou, 2009).

Table 2 displays the number of observational studies published since 1995 reporting a benefit of dietary n-3 PUFA, fish or cod liver oil intake. Of the 16 studies which investigated the relationship between dietary fish or seafood intake and mood, 12 (75%) reported a benefit (Hibbeln, 1998; Tanskanen, Hibbeln, Hintikka, Haatainen, Honkalampi, & Viinamaki, 2001a; Tanskanen, Hibbeln, Tuomilehto, Uutela, Haukkala, Viinamaki *et al*., 2001b; Silvers & Scott, 2002; Noaghiul & Hibbeln, 2003; Peet, 2004; Timonen, Horrobin, Jokelainen, Laitinen, Herva, & Rasanen, 2004; Barberger-Gateau, Jutand, Letenneur, Larrieu, Tavernier, & Berr, 2005; Appleton, Peters, Hayward, Heatherley, McNaughton, Rogers *et al*., 2007a; Appleton, Woodside, Yarnell, Arveiler, Haas, Amouyel *et al*., 2007b; Astorg, Couthouis, Bertrais, Arnault, Meneton, Guesnet *et al*., 2008; Bountziouka, Polychronopoulos, Zeimbekis, Papavenetiou, Ladoukaki, Papairakleous *et al*., 2009), of which eight employed a cross-sectional design. One of these studies reported a significant association in females only (Timonen *et al*., 2004), while in another, the significant negative association between dietary fish intake and depressive symptoms became nonsignificant after adjustment for confounders (Appleton *et al*., 2007a). Seven of the studies that described a benefit of dietary fish or seafood intake used mood questionnaires as outcome measures, while three used a diagnosis of clinical depression, one used a diagnosis of bipolar disorder and one used antidepressant prescription. One Norwegian cross-sectional study (Raeder, Steen, Vollset, & Bjelland, 2007) reported a reduced risk of depressive symptoms among daily cod liver oil consumers. With regard to the relationship between n-3 PUFA and mood, only total n-3 PUFA and ALA demonstrated a convincing benefit, with five (Edwards, Peet, Shay, & Horrobin, 1998; Suzuki, Akechi, Kobayashi, Taniguchi, Goto, Sasaki *et al*., 2004; Kamphuis, Geerlings, Tijhuis, Kalmijn, Grobbee, & Kromhout, 2006; Astorg *et al*., 2008; Clayton, Hanstock, Hirneth, Kable, Garg, & Hazell, 2008) out of seven (Edwards *et al*., 1998; Suzuki *et al*., 2004; Kamphuis *et al*., 2006; Astorg *et al*., 2008; Clayton *et al*., 2008; Heath & Berman, 2008; Murakami *et al*., 2008) studies reporting a significant advantage of high dietary total n-3 PUFA and two out of three reporting a significant advantage of high dietary ALA (Edwards *et al*., 1998; Suzuki *et al*., 2004). Only one of five studies that investigated the effect of DHA or n-3 eicosapentaenoic acid (EPA) on mood outcomes reported a significant benefit (Clayton *et al*., 2008), while only one of two studies that considered DHA and EPA in combination observed a beneficial effect (Colangelo, He, Whooley, Daviglus, & Liu, 2009).

Of the 26 papers which considered dietary fish, cod liver oil or n-3 PUFA intake on mood, the two which employed a case control methodology reported a beneficial effect of n-3 PUFA on depressive symptoms (Edwards *et al*., 1998; Clayton *et al*., 2008), despite comprising relatively low sample sizes. All three ecological studies also observed an inverse relationship between fish consumption and mood (Hibbeln, 1998; Noaghiul & Hibbeln, 2003; Peet, 2004). Although the majority of the cross-sectional studies (79%) showed an inverse relationship between n-3 PUFA and mood, only 29% of the cohort studies showed a significant effect. The cross-sectional studies were generally well-powered; the smallest sample size (Oishi *et al*., 2009) comprising 279 participants. The three cohort studies with sample sizes of less than 1,000 participants (Jacka *et al*., 2004; Kyrozis *et al*., 2009; Schiepers *et al*., 2009) failed to observe a benefit of n-3 PUFA on mood, although the two largest cohort studies also did not observe a significant association.

One cross-sectional study quantified n-6 PUFA (Wolfe, Ogbonna, Lim, Li, & Zhang, 2009), and found that high LA was associated with an increased risk of depressive symptoms as measured by the CES-D.

Biomarker Studies: Of the 39 studies which investigated the relationship between fatty acid biomarkers and mood, 14 employed a case-control design, 24 were cross-sectional and one was a cohort study. Five studies (13%; four cross-sectional and one case-control), with relatively small sample sizes, reported no significant associations (Mahadik, Mukherjee, Horrobin, Jenkins, Correnti, & Scheffer, 1996; Assies, Lok, Bockting, Weverling, Lieverse, Visser *et al*., 2004; Kiecolt-Glaser, Belury, Porter, Beversdorf, Lemeshow, & Glaser, 2007; Appleton, Gunnell, Peters, Ness, Kessler, & Rogers, 2008; Aupperle, Denney, Lynch, Carlson, & Sullivan, 2008). In a further study, significant relationships were observed only between depression and various ratios within the n-3 and n-6 series (i.e. dihomo-gamma-linoleic acid (dGLA):gamma-linoleic acid (GLA), dGLA+docosapentaenoic acid(DPA):GLA+EPA and DPA:EPA) in adolescent adipose tissue (Mamalakis, Kiriakakis, Tsibinos, & Kafatos, 2004a).

Table 1. The number of hits returned, and the number of hits that met the inclusion criteria, for each database searched.

Database	Hits	Met inclusion criteria
EMBASE	1,446	62
MEDLINE	941	60
PsycINFO	271	32
ISI Web of Science	2,340	68

Table 2. The number of studies reporting a significant benefit of dietary fish, cod liver oil or n-3 PUFA intake. The total number of studies which reported a significant benefit are displayed, in addition to the number of studies reporting a benefit of dietary fish, cod liver oil or n-3 PUFA intake which employed a case-control, cross-sectional, ecological or cohort design.

		Studies reporting significant benefit				
Dietary Predictor	Number of studies	Total (%)	Case-control	Cross-sectional	Ecological	Cohort
Dietary fish/seafood intake	16	12 (75%)	0	8	3	1
Cod liver oil intake	1	1 (100%)	0	1	0	0
Total n-3 PUFA	7	5 (71%)	2	2	0	1
ALA	3	2 (67%)	1	1	0	0
DHA	5	1 (20%)	1	0	0	0
EPA	5	1 (20%)	1	0	0	0
DHA+EPA	2	1 (50%)	0	0	0	1
Overall (excludes n-6)	26	18 (69%)	2/2 (100%)	11/14 (79%)	3/3 (100%)	2/7 (29%)

Table 3. The number of studies reporting a significant benefit n-3 PUFA biomarker status. The total number of studies which reported a significant benefit are displayed, in addition to the number of studies reporting a benefit of n-3 PUFA status which employed a case-control, cross-sectional or cohort design.

		Studies reporting significant benefit			
Fatty acid	Number of studies	Total (%)	Case-control	Cross-sectional	Cohort
ALA	22	6 (27%)	3	3	0
DHA	37	16 (43%)	8	7	1
DPA	25	7 (28%)	4	3	0
EPA	35	10 (29%)	6	4	0
DHA+EPA	3	2 (67%)	1	1	0
AA:DHA	7	2 (29%)	1	1	0
AA:EPA	15	8 (53%)	4	4	0
osbond acid:DHA	2	1 (50%)	1	0	0
Total n-6:Total n-3	15	6 (40%)	3	3	0
Total n-3 PUFA	24	11 (46%)	8	3	0
Overall (excludes n-6)	39	32 (82%)	12/14 (86%)	19/24 (79%)	1/1 (100%)

Table 3 displays the number of studies which found a benefit of n-3 PUFA biomarker status on mood outcomes. Six (22%; Edwards *et al*., 1998; Maes, Christophe, Delanghe, Altamura, Neels, & Meltzer, 1999; Ranjekar, Hinge, Hegde, Ghate, Kale, Sitasawad *et al*., 2003; Mamalakis, Kiriakakis, Tsibinos, & Kafatos, 2004b; Mamalakis, Jansen, Cremers, Kiriakakis, Tsibinos, & Kafatos, 2006a; Mamalakis, Kiriakakis, Tsibinos, Jansen, Cremers, Strien *et al*., 2008) observed that higher ALA status was associated with better mood outcomes; with a similar pattern of results observed for 16 (43%; Edwards *et al*., 1998; Peet, Murphy, Shay, & Horrobin, 1998; Mamalakis, Tornaritis, & Kafatos, 2002; Chiu, Huang, Su, Lu, Huang, Chen *et al*., 2003; Tiemeier, van Tuijl, Hofman, Kiliaan, & Breteler, 2003; Frasure-Smith, Lespérance, & Julien, 2004; Kobayakawa, Yamawaki, Hamazaki, Akechi, Inagaki, & Uchitomi, 2005; Mamalakis, Kalogeropoulos, Andrikopoulos, Hatzis, Kromhout, Moschandreas *et al*., 2006b; Parker, Heruc, Hilton, Olley, Brotchie, Hadzi-Pavlovic *et al*., 2006; Conklin, Harris, Manuck, Yao, Hibbeln, & Muldoon, 2007a; McNamara, Hahn, Jandacek, Rider, Tso, Stanford *et al*., 2007; Amin, Menon, Reid, Harris, & Spertus, 2008; Clayton *et al*., 2008; McNamara, Jandacek, Rider, Tso, Stanford, Hahn *et al*., 2008; Sarri, Linardakis, Tzanakis, & Kafatos, 2008; Schiepers *et al*., 2009) which investigated DHA, seven (28%; Adams, Lawson, Sanigorski, & Sinclair, 1996; Edwards *et al*., 1998; Peet *et al*., 1998; Maes *et al*., 1999; Kobayakawa *et al*., 2005; Mamalakis *et al*., 2006b; Amin *et al*., 2008) which investigated DPA and 10 (29%; Adams *et al*., 1996; Maes, Smith, Christophe, Cosyns, Desnyder, & Meltzer, 1996; Edwards *et al*., 1998; Maes *et al*., 1999; Ranjekar *et al*., 2003; Mamalakis, Kiriakakis, Tsibinos, Hatzis, Flouri, Mantzoros *et al*., 2006c; Conklin *et al*., 2007a; Sublette, Francesca, James, Kaizong, Jane, Stephanie *et al*., 2007; Clayton *et al*., 2008; Feart, Peuchant, Letenneur, Samieri, Montagnier, Fourrier-Reglat *et al*., 2008) which investigated EPA. In one study (Clayton *et al*., 2008), the observation that erythrocyte EPA and DHA were lower in patients with juvenile bipolar disorder, relative to healthy controls, became nonsignificant after adjustment for fatty acid intake. In addition, the negative relationship between self-reported depressive symptoms and DPA status reported by Mamalakis and colleagues (Mamalakis *et al*., 2006b), became nonsignificant after adjustment for a number of potentially confounding variables. Phospholipid DPA was found to be higher in patients meeting DSM-IV criteria for major depression, relative to controls, but this finding became nonsignificant after Bonferroni adjustment for multiple comparisons (Peet *et al*., 1998).

Of the three studies which investigated the relationship between DHA and EPA combined and mood outcomes, one case control study (Frasure-Smith *et al*., 2004) observed that DHA+EPA status was lower in patients with major depression than controls, while one cross-sectional investigation (Ali, Garg, Cohen, Bhave, Harris, & Whooley, 2009) found a negative association between depressive symptoms and DHA+EPA status in patients with coronary heart disease (although this relationship became nonsignificant after adjustment for potential confounders). A cross-sectional study (Philibert, Bouchard, & Mergler, 2008) reported a positive relationship between serum DHA+EPA status in habitual fish consumers and depressive symptoms in male participants only.

The question of whether fatty acids influence mood was tested using various ratios of n-6:n-3 PUFA status. Of the seven studies that investigated the role of a low AA:DHA or a high DHA:AA ratio in modulating mood, two (29%; Tiemeier *et al*., 2003; Frasure-Smith *et al*., 2004) reported a benefit. Similar findings were reported for eight (53%; Adams *et al*., 1996; Maes *et al*., 1996; Maes *et al*., 1999; Frasure-Smith *et al*., 2004; Conklin, Manuck, Yao, Flory, Hibbeln, & Muldoon, 2007b; Crowe, Skeaff, Green, & Gray, 2007; Schins, Crijns, Brummer, Wichers, Lousberg, Celis *et al*., 2007; Sublette *et al*., 2007) that investigated the AA:EPA or EPA:AA ratio, one (Maes *et al*., 1999) of two studies that investigated the osbond acid (n-6 DPA):DHA or DHA: osbond acid ratio and six (40%; Adams *et al*., 1996; Maes *et al*., 1996; Maes *et al*., 1999; Tiemeier *et al*., 2003; Frasure-Smith *et al*., 2004; Mamalakis *et al*., 2004b) that investigated the total n-6 PUFA: total n-3 PUFA or total n-3 PUFA: total n-6 PUFA ratio. One (Dinan, Siggins, Scully, O'Brien, Ross, & Stanton, 2009) found the opposite relationship for EPA:AA ratio status, in that the plasma EPA:AA ratio was higher in a subgroup of major depressed patients who did not respond to a selective serotonin reuptake inhibitor (SSRI) intervention, relative to healthy controls. Of the 24 reports that investigated the relationship between all of the fatty acids within the n-3 series in combination on mood outcomes, 46% demonstrated a benefit (Maes *et al*., 1996; Edwards *et al*., 1998; Peet *et al*., 1998; Maes *et al*., 1999; Ranjekar *et al*., 2003; Frasure-Smith *et al*., 2004; Kobayakawa *et al*., 2005; Mamalakis *et al*., 2006a; Garland, Hallahan, McNamara, Carney, Grimes, Hibbeln *et al*., 2007; Amin *et al*., 2008; Clayton *et al*., 2008).

With regard to design, only one study employed a longitudinal methodology (Schiepers *et al*., 2009). Despite the relatively small sample size for an investigation of this design (*N*=241), an inverse relationship was reported between depressive symptoms and phospholipid DHA, only in the subgroup of participants with more severe depressive symptoms. In addition, 86% of the case-control and 79% of the cross-sectional studies reported a significant inverse relationship between n-3 PUFA status and mood. The sample sizes of the case-control and cross-sectional studies which investigated the relationship between n-3 PUFA status and mood were generally smaller than the dietary ones. However, sample size appears to influence the likelihood of observing an association between n-3 PUFA status and mood, with only two cross-sectional, and no case-control studies with a sample size over 100 not observing a significant inverse relationship.

The relatively fewer papers which found that n-6 PUFA status influenced mood reported mixed findings. One cross-sectional study observed that total plasma n-6 PUFA was negatively associated with Beck Depression Inventory (BDI) scores in healthy individuals and individuals presenting to a hospital emergency department following self-harm (Garland *et al*., 2007). Two cross-sectional (Tiemeier *et al*., 2003; Conklin *et al*., 2007b) and one case-control study (Dinan *et al*., 2009) reported that lower AA was associated with better mood, while three case-control investigations reported the inverse (Chiu *et al*., 2003; Sublette *et al*., 2007; McNamara *et al*., 2008). A further cross-sectional study (Mamalakis *et al*., 2006c) observed a positive relationship between adipose tissue dGLA and depressive symptoms as measured by the CES-D, while a case-control (Peet *et al*., 1998) and two cross-sectional studies (Mamalakis *et al*., 2002; Amin *et al*., 2008) reported that higher dGLA was associated with better mood outcomes. However, in the study by Mamalakis and colleagues (Mamalakis *et al*., 2002), the result became nonsignificant after adjustment for potential confounders. Likewise in the study by Peet and colleagues (Peet *et al*., 1998), the finding became nonsignificant after Bonferroni adjustment for multiple comparisons. This latter report (Peet *et al*., 1998) also found that LA was higher in controls relative to cases, a result that was again nonsignificant after Bonferroni adjustment. A negative association was observed between adipose tissue LA and scores on the Geriatric Depression Scale in a cross-sectional Greek sample of elderly males (Mamalakis *et al*.,

2004b). A further case-control study reported that plasma phospholipid GLA and adrenic acid were higher in patients with a diagnosis of major depression relative to controls (Frasure-Smith *et al*., 2004), two months following acute coronary syndrome. A cross-sectional investigation observed a negative relationship between BDI scores and adipose tissue eicosadienoic acid, which was nonsignificant following adjustment for potentially confounding factors (Mamalakis *et al*., 2008). No papers which observed a significant relationship between n-6 PUFA and mood employed a longitudinal design.

Suicidality/self-harm studies: Of the seven studies which investigated the relationship between fish intake, PUFA intake or PUFA status and suicidality or self-harm, two from Finland focussed specifically on dietary fish intake. Both were cross-sectional studies (Tanskanen *et al*., 2001a; Timonen *et al*., 2004), and reported a reduced risk of suicidal ideation in frequent fish consumers. Interestingly, the relationship was significant only in females in the study of Timonen and colleagues (Timonen *et al*., 2004). Of the four studies that measured fatty acid status using various biomarkers, a cohort (Sublette, Hibbeln, Galfalvy, Oquendo, & Mann, 2006) and two case-control (Huan, Hamazaki, Sun, Itomura, Liu, Kang *et al*., 2004; Garland *et al*., 2007) studies reported a benefit of DHA, one paper reported a benefit of DPA (Huan *et al*., 2004) and two reported a benefit of EPA (Huan *et al*., 2004; Garland *et al*., 2007). The two case-control studies (Huan *et al*., 2004; Garland *et al*., 2007) found an association between lower total n-3 PUFA and attempted suicide/self-harm; likewise n-6:n-3 ratio was higher in suicide attempters, relative to controls (Huan *et al*., 2004) and the cohort study revealed that a high n-6:n-3 ratio predicted suicide attempt (Sublette *et al*., 2006). With regard to the n-6 series, a case-control study (Garland *et al*., 2007) observed that plasma LA and total n-6 PUFA were lower in patients presenting to a hospital emergency department for treatment for self-harm, relative to controls. One Finnish cohort study comprising 29,133 males failed to observe any associations between dietary n-3 PUFA intake and death by suicide during the follow-up interval (Hakkarainen *et al*., 2004). Similarly, a case-control study failed to find significant differences in post-mortem orbitofrontal brain tissue fatty acid accretion between suicide victims and controls (McNamara, Jandacek, Rider, Tso, Dwivedi, Roberts *et al*., 2009).

Perinatal depression studies: There were six papers published on the relationship between dietary fish/n-3 PUFA intake and perinatal depression. Higher seafood intake was associated with lower national postpartum depression prevalence in an ecological study (Hibbeln, 2002). A large (*N*=54,202) cohort study found an association between prescription of antidepressant medication and lower dietary fish intake in new mothers (Strom, Mortensen, Halldorsson, Thorsdottir, & Olsen, 2009). A further large (*N*=14,541) cross-sectional analysis observed a reduced risk of postpartum depression with higher dietary n-3 intake from seafood (Golding, Steer, Emmett, Davis, & Hibbeln, 2009). By contrast, case-control (Browne, Scott, & Silvers, 2006), cross-sectional (Sontrop, Avison, Evers, Speechley, & Campbell, 2008) and cohort studies (Miyake, Sasaki, Yokoyama, Tanaka, Ohya, Fukushima *et al*., 2006) failed to show a relationship between dietary fish/n-3 PUFA intake and perinatal depression.

The relationship between n-3 PUFA status using various biomarkers and perinatal depression was reported in five studies. In an ecological analysis (Hibbeln, 2002), higher DHA in breast milk was associated with lower national postpartum depression prevalence. In addition, postpartum depression was associated with lower DHA, lower total n-3 PUFA and a higher n-6 PUFA:n-3 PUFA ratio in case-control (Rees, Austin, Owen, & Parker, 2009) and cross-sectional (De Vriese, Christophe, & Maes, 2003) studies. Further case-control (Browne *et al*., 2006) and cohort (Otto, de Groot, & Hornstra, 2003) studies did not observe a significant relationship between postpartum depression and fatty acid status, although the cohort study (Otto *et al*., 2003) reported an improvement in the DHA:osbond acid ratio during the 32 week period following delivery for those participants with a BDI score of less than 10. The two cohort studies with a sample size of less than 1,000 individuals (Otto *et al*., 2003; Miyake *et al*., 2006), did not yield a significant relationship.

DISCUSSION

The majority of papers included in this review (84%) were published after 2003, demonstrating that research interest concerning the relationship between essential fatty acids and mood has vastly increased in recent years. This may be due to increased demand for scientifically insightful information relating to the efficacy of essential fatty acids, as well as from heightened awareness of the potential health benefits of n-3 PUFA and the high prevalence rate of mood disorders in the community (Kessler *et al*., 2005).

Therefore, this review is timely, and it is necessary to systematically and inclusively review the burgeoning literature of observational papers which have been published in this area over the past 15 years.

Fish intake was most beneficial in studies that investigated the association between dietary PUFA and mood. A benefit of cod liver oil intake, total dietary n-3 PUFA and ALA was also observed, although these studies were fewer in number. Despite the weight of evidence that dietary fish intake likely provides considerable benefit to mood, one cannot exclude that these effects may be due in part to nutritional factors that are unrelated to PUFA. A considerable proportion (69%) of studies which investigated the relationship between dietary fish, cod liver oil or n-3 PUFA intake reported an inverse relationship between intake and mood. The one study that quantified dietary intake of an n-6 fatty acid (LA) suggested that high n-6 PUFA intake may be associated with poor mood outcomes (Wolfe *et al*., 2009).

With respect to those studies that investigated the relationship between fatty acid status and mood, the most reliable measure in terms of mood enhancement appeared to be a lower ratio of AA to EPA. The ratio of osbond acid to DHA and the combined DHA and EPA status were the only other n-3 PUFA predictors to benefit mood in 50% or more of the studies in which they were measured, however these two variables were quantified in substantially fewer studies. The number of studies which found a significant benefit of DHA status on mood was also large (43%), suggesting that further research into the role of DHA on mood is warranted. Design did not appear to be an influencing factor, with case-control and cross-sectional studies well represented among those studies for which the mood enhancing properties of n-3 PUFA status was demonstrated. Overall, a large number of the studies which investigated n-3 PUFA status and mood (82%) offered support for an inverse relationship. While causality is difficult to attribute in the many cross-sectional and case-control studies conducted, this finding suggests that a low n-3 PUFA status may be detrimental in terms of mood. Relative to n-3 PUFA, there were fewer investigations of the associations between n-6 PUFA biomarkers and mood. The findings reported were equivocal, and it is difficult to conclude that n-6 PUFA status affects mood.

The majority of the papers that investigated the association between PUFA intake or status and suicidality or self-harm reported a significant benefit of n-3 PUFA or dietary fish intake. Only two of the seven studies in this category failed to report a significant effect (Hakkarainen *et al*., 2004; McNamara *et al*., 2009), despite the relative heterogeneity regarding the methods employed by the suicidality and self-harm investigations. However, one of those showing no effect was by far the largest study in this category, involving over 29,000 males. High fish intake and high levels of n-3 PUFA therefore appear to be of uncertain benefit in the context of reducing suicidality and self-harm.

The association between PUFA intake or status and perinatal depression was also uncertain, with only five of eight studies reporting a significant benefit of n-3 PUFA or fish intake. However, disparate methodologies were employed between these investigations, both in terms of the determination of fatty acid intake or status and the method by which perinatal depression was defined.

Dietary studies predominantly employed a cross-sectional design. A weakness of the cross-sectional, and indeed the case-control design, is that these methodologies do not enable ‘cause and effect’ to be addressed (Bonita, Beaglehole, & Kjellström, 2006). Therefore, it cannot be reliably determined whether high intake of n-3 PUFA benefits mood, or whether individuals with a more positive affect consume more n-3 PUFA. The case-control design is particularly problematic, given that those individuals with a diagnosed mood disorder may have different dietary behaviours relative to healthy controls. By contrast, cohort studies are able to address the question of causality (Bonita *et al*., 2006). However, only two dietary investigations out of the seven cohort studies that were conducted actually observed a benefit of n-3 PUFA on mood. This may have been an issue of power, given that the three cohort studies with relatively small sample sizes failed to observe a significant effect. However, the two largest investigations (in terms of sample size) also did not report a significant relationship. The three studies which undertook an ecological analysis of dietary fish intake and mood (Hibbeln, 1998; Noaghiul & Hibbeln, 2003; Peet, 2004) all observed an inverse relationship. However, while useful for generating hypotheses, conclusions drawn from ecological studies should be treated with caution, given that a large number of cultural differences in addition to fish intake are also likely to influence mood. In fact, colinearity between n-3 PUFA intake and a range of lifestyle factors could potentially confound studies which have investigated the relationship between n-3

PUFA intake and mood. Therefore, the findings of those reports which have failed to adjust for potential confounders should be treated with caution (see Supplementary Tables 1-4 for details of those papers which adjusted for confounders). In terms of the biomarker category, case-control and cross-sectional designs were both widely employed. However, only one cohort study was conducted. These findings demonstrate that additional longitudinal investigations are clearly needed in order to reliably determine causality in the relationship between n-3 PUFA and mood. Statistical power appeared to be an issue in biomarker studies with small sample sizes. Only two biomarker studies with a sample size of more than 100 did not observe a significant relationship in the expected direction.

Several studies were conducted in countries with a high national seafood intake. This may be due to a relatively greater research interest in these countries of the potential benefits of fish and n-3 PUFA intake on health outcomes. Nonsignficant relationships were reported for an equivalent number of dietary studies which were conducted in countries with a high seafood and countries with a relatively lower average seafood intake. This suggests that the overall findings were not influenced by the country of origin of the particular studies. This is relevant, given that a threshold effect may be expected, whereby once omega-3 intake or status reaches a certain level, no further mood benefits would be detectable. However, this does not appear to be the case here.

A number of mechanisms have been proposed to explain the relationship between PUFA intake or status and mood disorders. These include, but are not limited to, the actions of essential fatty acids on inflammation, neurotransmitter synthesis and regulation of gene transcription in the CNS (Alessandri *et al*., 2004; Young & Conquer, 2005). None of the studies reviewed specifically investigated whether any of these mechanisms contributed to the relationships observed between essential fatty acids and mood. This is likely due to the fact that such mechanistic studies would be carried out in animal models and in vitro experiments, which are not included in this review. Studies addressing the mechanisms underlying the relationship between essential fatty acids and mood are required in order to fully understand the nature of this association, and should be the focus of future empirical investigations.

A limitation of this review relates to the heterogeneity of studies included in terms of design, sample size, PUFA measurement and mood measurement. Rather than apply strict inclusion criteria to eliminate those papers which may not have employed an optimal methodology, we chose broad inclusion criteria to ensure that all observational investigations addressing the question of whether essential fatty acids modulate mood were incorporated. We have distinguished between those studies that measured PUFA intake and those which quantified PUFA status using a range of biomarkers. While fatty acid intake and status are undoubtedly related, individual differences in fatty acid absorption, transport, uptake, metabolism and excretion can influence this relationship (Arab & Akbar, 2002), which is the reason that we have treated intake and status separately in the present review. Within each of these categories, a variety of methodologies were used. The biomarker studies employed numerous different methods to measure PUFA status, which could potentially result in markedly different outcomes. For example, plasma phospholipid concentrations of PUFA are purported to reflect intake over the preceding 14 days, whereas erythrocyte concentrations are representative of intake over a longer timeframe (Clayton *et al*., 2008). Adipose tissue PUFA concentrations reflect an even longer-term intake (Arab & Akbar, 2002). However, a comparison of the methods used by the individual studies to quantify essential fatty acid status did not appear to influence the likelihood of a significant relationship between fatty acid status and mood. Further, a number of different designs were employed, including case-control, cross-sectional, ecological and longitudinal, and sample sizes varied widely between studies. Some of the larger investigations comprised more than 20,000 participants, with ecological analyses using population data from several countries. Smaller studies comprised less than 50 participants and others included participants with underlying comorbidities such as cardiovascular and cancer related illnesses, which may have their own relationship with mood.

Another limitation of this review is that reports which included mood disorder patients as all or part of the participant group were not distinguished from those which included only healthy individuals. This was due to the fact that divergent criteria were used in defining whether participants had a mood disorder, rendering such an analysis problematic. A further consideration with systematic reviews more generally, is that the reported effects may be overstated due to a publication bias, whereby papers which demonstrate significant effects are more likely to be published.

In this systematic review, we present an unbiased analysis of all observational papers which have investigated the relationship between essential fatty acids and mood between 1995 and 2009. The inclusion of only observational studies has eliminated a number of heterogeneous factors associated with randomised controlled trials, including the supplementation dosage, duration, composition and compliance, which render the comparison of different studies difficult. Additionally, the observational methodologies employed by those studies reviewed here enabled the long-term investigation of the association between n-3 PUFA and mood in the general population, given the short-term nature of supplementation trials. The conclusions drawn from this review reflect those of previous systematic reviews of intervention trials (Appleton *et al*., 2006; Williams *et al*., 2006), suggesting a relationship between essential fatty acids and mood. Therefore, on the basis of those studies reviewed here, it can be concluded that long-term exposure to n-3 PUFA can also benefit mood. However, the specific nature of this relationship remains uncertain. Further research is required to enable a better understanding of the relationships between fatty acids and mood, and to determine the mechanisms that underlie these relationships.

In summary, there has been an increase in the number of observational studies in humans investigating essential fatty acids and mood in the past 15 years. Evidence from the present review has demonstrated that on the basis of these previous studies, a relationship may exist between essential fatty acids and depression. Of all of the variables that were used as measures of PUFA intake or status, dietary fish intake was most convincingly associated with mood, but less clearly with major outcomes such as suicide. There is a clear need for further longitudinal investigations to be conducted in this area, in order for causality to be reliably determined.

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SPECIAL NOTE:

'Supplementary tables can be obtained by emailing the corresponding author wendyo@ichr.uwa.edu.au.

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