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Review article

Nutrition, mood and behaviour: a review

Soh N, Walter G, Baur L, Collins C. Nutrition, mood and behaviour: a review.

Objective: To conduct a critical review of recent empirical research regarding mood, behaviour and nutrition factors including essential fatty acids, macronutrients, micronutrients and food additives.
Method: A literature search of databases Medline, PsycInfo, CINAHL and Embase up to October 2008. The search emphasised empirical research published in the last 10 years and also included older literature. Studies in both adults and children were addressed.
Results: Research into omega-3 fatty acids has been substantial but evidence for their potential in treating mood and behaviour is modest. In comparison, there has been much less research into carbohydrate and protein intakes and little evidence for their ability to influence mood and behaviour. Recent trials with food additives suggest their removal from the diet may benefit susceptible children with hyperactivity disorders. Micronutrient supplementation appears to improve mood only in those who were initially deficient in micronutrients.
Conclusions: More stringent research designs such as longitudinal studies and the use of biologically inert placebos within randomised controlled trials are needed before supplemental use of omega-3 fatty acids to treat disorders of mood and behaviour can be recommended. Caution is advised regarding the indiscriminate use of diets free of artificial food additives in managing hyperactivity disorders, as they may place an undue burden on individuals and their families. Should omega-3 fatty acid supplementation or the elimination of certain food additives be established as effective, they may provide cost-effective, accessible and well-tolerated adjuncts to standard psychiatric treatments for mood and behavioural disturbances.

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Introduction

There is a strong and growing community interest in the effects of nutrition and dietary factors on mental health. Notwithstanding recent interest in how diet may influence the aetiology of depression (1), relatively little research has been conducted in the relationship between mental health and nutritional factors, apart from extensive studies on eating disorders. This is somewhat surprising, given the current high prevalence of psychiatric disorders, with depressive and anxiety disorders reported at 5–29% (2–5), and the morbidity and mortality associated with those disorders. In addition, behavioural disorders, especially attention deficit hyperactivity disorder (ADHD), are of particular concern in children (3,6,7).

This focused review examines dietary components that have potential effects on mood and behaviour in humans, and their possible therapeutic uses. Dietary fat and omega-3 fatty acids, dietary protein and carbohydrate, food additives and micronutrients are considered in turn. The databases Medline, PsycInfo, CINAHL and Embase were searched using the keywords depression, anxiety, affective disorders, ADHD, mood, behaviour, conduct disorder and learning disorder, in conjunction with nutrition, diet, fatty acids, omega-3, food additives, food preservatives, food colourings, sucrose and tryptophan. Citations were searched up to October 2008, with an emphasis on empirical studies published within the last 10 years. This review does not address dietary effects on cognition, the impact of mental health itself on nutrition status or the role of obesity in mood and behaviour.

Dietary fat and omega-3 fatty acids

The focus of most studies on dietary fat and mental health has been on omega-3 fatty acids. Omega-3

fats, in particular the long-chain fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are purported to play a role in ADHD, depression and bipolar disorder. Epidemiological studies report an association between lower prevalences of bipolar and mood disorders and higher fish consumption (8–12), with oily fish being a source of long-chain omega-3 fatty acids, although not all studies support this (8,11). Most studies assess fatty acid levels in plasma or erythrocyte membrane and there is evidence of a positive association between erythrocyte membrane DHA levels and the DHA content of brain tissue (13). This section discusses essential fatty acids and bipolar disorder, depression, depression in pregnancy, postpartum depression and ADHD.

Bipolar disorder

Low plasma omega-3 and high omega-6 levels are familial trait markers for bipolar disorder (14), and there is interest in the use of omega-3 fats in treating bipolar disorder. Results of recent studies are mixed. In an open-label pilot study, 2000 mg EPA/day resulted in 50% or greater decrease in Hamilton Depression Rating Scale scores for 7 out of 10 patients with bipolar disorder after 1 month, but also raised concerns regarding what the optimal dose of EPA is and the duration required to show improvement (15). In contrast, 6000 mg/day ethyl-EPA had little effect compared with a liquid paraffin placebo in individuals with bipolar depression or rapid cycling bipolar disorder (16). The study questioned whether DHA needed to be included in treatments and also what the optimal dosage would be (16). However, this double-blind randomised controlled trial (RCT) also had a high attrition rate (54%) and required individuals not to change the dose of their mood stabiliser medications throughout the trial. In an older RCT, 6200 mg EPA and 3400 mg DHA/day, which is comparatively a high dose to that used in other studies, resulted in significantly longer remission in bipolar disorder than a placebo of olive oil esters, no matter whether the participants were taking medication (17).

Only a few studies examine the association between essential fatty acids and symptoms of mania. More severe manic symptoms correlated negatively with free plasma arachidonic acid (an omega-6 fatty acid) and EPA, including after adjustment for depression levels, in a small sample of patients with acute manic episodes (18). The severity of depressive symptoms correlated positively with arachidonic acid:EPA ratios in this sample (18). Aside from the small sample size, the authors noted difficulties in recruiting participants with bipolar disorder who had acute mania and it was likely that individuals with the most severe symptoms were not sampled (18). In another study, depressive symptoms were significantly reduced from baseline by 1000 and 2000 mg/day ethyl-EPA as adjunctive treatment in individuals with bipolar disorder compared with a paraffin oil placebo, after 12 weeks in an RCT but there was no difference in manic symptoms (19). There was no difference between the two ethyl-EPA dosages in the level of improvement and no difference across the two ethyl-EPA groups and placebo group in symptom severity at 12 weeks. While participants in this trial did not have particularly severe symptoms, 12 out of the 26 participants on placebo needed their medication adjusted because of deterioration in their mental state or side effects during the trial, while only 7 of the 24 on 1000 mg ethyl-EPA and 7 out of the 25 on 2000 mg ethyl-EPA needed their medication adjusted, implying ethyl-EPA yielded a greater response than placebo (19). Prior to this, a double-blind placebo-controlled trial in 14 patients with bipolar disorder found manic symptoms in both treatment (440 mg EPA and 240 mg DHA/day as an adjunct to valproate) and placebo groups (olive oil and valproate) improved significantly from baseline (20). There was no difference in symptom severity between the treatment and placebo group throughout the trial, but it was relatively short, at just four weeks' duration, and the doses of omega-3 were low compared with other trials.

Few studies have investigated omega-3 fatty acids and bipolar disorder in children, but some have been recently published. Among them are an open-label pilot study of 1290–4300 mg EPA and DHA/day in 16 paediatric patients, showed significant improvement in symptoms after 8 weeks (21). However, the actual dose of omega-3 used varied and depended on clinical judgement and both manic and depressive symptoms were still present at the end of the trial. In a larger RCT of 44 children with bipolar disorder, flax oil, a source of omega-3 alpha-linolenic acid, did not improve mood compared with the olive oil placebo (22). The results are confounded as the duration of the trial varied (2–16 weeks), some children were taking psychotropic medication and the dose of flax oil varied over the trial, providing 550 to 6000 mg alpha-linolenic acid/day.

Depression

There is an association between lowered omega-3 status and depressive symptoms, which appears more pronounced in severe or recurrent depression than in milder or single-episode depression (23). Postmortem DHA content of the orbital frontal cortex

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of individuals with major depressive disorder are significantly lower compared with controls (24), but the study sample size was small and there was no information on the participants' diet, and therefore omega-3 intake, prior to death or whether the sample was representative of all major depressive disorder patients. Additionally, the severity of the symptoms was also not known. Recently, no association between depression scores and plasma omega-6:omega-3 ratios, arachidonic acid:EPA, arachidonic acid:DHA, total omega-3, alpha-linolenic acid, EPA or DHA levels was observed in 192 community adults (25). However, this sample, while low consumers of omega-3 fatty acids, had only mild to moderate levels of depression and omega-3 status may be more important in a clinical setting or in more severe depression (25). A slightly older study found significantly higher plasma arachidonic acid:EPA ratios in post-myocardial infarction (MI) patients with depression compared with those without depression (26). Similarly, in patients with MI and unstable angina, those with major depression had higher plasma omega-6:omega-3 fatty acid ratios and lower plasma DHA and total omega-3 compared with those without major depression in a study published in 2004 (27). Again, neither study measured dietary intake.

Regional differences in diet and lifestyle may confound the association between depression and omega-3 fatty acid status. For example, there is no significant association between dietary omega-3 intake and the prevalence of depression in community-dwelling adults in Japan (28), but the intake of fish and seafood in Japan is generally high (29). In rural Greece, where the prevalence of depressive symptoms is low, no association was found between adipose levels of omega-3 fatty acids and depression levels, although the overall diet and lifestyle are not comparable to those of north Europe or the United States (30). Essential fatty acid metabolism may also be disturbed in individuals with depression. There were no differences in dietary omega-3 as a proportion of energy intake or erythrocyte omega-6 as a fraction of phospholipid content between 10 patients with major depressive disorder and 14 matched healthy controls, but erythrocyte membrane levels of omega-3 were significantly lower in patients (31). Reduced DHA levels and increased linoleic acid were significant predictors of greater symptom severity across the entire sample and, within the patient group itself, dietary omega-3 was significantly associated with the severity of depression. This study had the advantage of rigorous dietary assessment, using a 7-day weighed food record to measure omega-3 intake. It would have been interesting to explore the relationship between clinical status and erythrocyte omega-3 on controlling for dietary intake and whether the relationship between dietary and erythrocyte omega-3 levels differs because of the presence or absence of major depressive disorder.

Intervention studies of omega-3 as a treatment for depression have produced mixed results and are difficult to interpret because of study design. Appleton et al. (32) observed there is presently limited empirical evidence for the effect of omega-3 on depressed mood. Their meta-analysis of 12 trials of omega-3 fatty acids in treating depressed mood reported that most trials were small, of short duration, used different combinations and doses of omega-3 fatty acids and were performed in heterogeneous samples. However, there is some evidence that omega-3 fatty acids have an effect in groups with major depression and that the effect is stronger compared with those with other form of depressive illness. A more recent analysis by Lin and Su (33) did not assess any trials newer than Appleton et al. had, but analysed the studies by different EPA dosages. EPA doses of 4000 mg/day or higher had significantly greater antidepressant effects than placebo, but the effects of doses of 2000 mg/day or less were not significantly different to placebo (33).

The use of omega-3 as an adjunct to antidepressant medication in major depressive disorder has also yielded mixed results. Adjunctive treatment with 2200 mg DHA and 600 mg EPA/day in adults had no benefit over an olive oil placebo in a 16-week double-blind RCT (34). In a slightly older trial which used a similar treatment combination of DHA and EPA with an olive oil placebo, mood improved in both treatment and placebo groups over 12 weeks but there was no difference between the two (35). It is not clear how severe the level of depression was, considering the participants were taking a constant dose of antidepressant medications for at least 2 months prior to the trial. Another study used a much higher dose of EPA (2200 mg DHA and 4400 mg EPA/day) and significantly reduced depressive symptoms compared with an olive oil esters placebo during the 8-week double-blind RCT (36). The rate at which depressive symptoms decreased was also significantly greater in the omega-3 group, even when controlling for antidepressant use. The treatment group's depression scores significantly decreased from baseline by the fourth week, although it was not stated whether the placebo group's scores were significantly lower than baseline at any timepoint. Although this latter study is older (2003) and the sample size is small, it had the advantage of assessing both dietary intake and tissue levels of omega-3. In this case, the frequency of fish and total unsaturated fatty acid intakes between placebo and omega-3 groups were similar, as were both groups' pre-treatment erythrocyte membrane

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contents of EPA and DHA. Various medications the patients taking were a confounding factor (36). In a 2002 study, adjunctive treatment with 2000 mg/day ethyl-EPA was associated with a significant and clinically meaningful decrease in depressive symptoms compared with placebo after a 4-week double-blind RCT (37).

Benefits of omega-3 supplements as a monotherapy are also unclear. A recent trial found significant improvement in patients with major depressive disorder following treatment with 1100 mg ethyl-EPA and 20 mg fluoxetine/day after 4 weeks, compared with ethyl-EPA and fluoxetine each as monotherapies (38). All three groups improved significantly from baseline as of week 2 (38).The improvement was sustained over weeks 6 and 8, but there was no difference between the two monotherapies. No placebo group was included because of ethical issues, leaving open the possibility of a placebo effect, but this study is the first to investigate EPA monotherapy. Other concerns include the small sample size of 16 subjects per group, the drop-out rate of 20%, and standard deviations or standard errors not being reported for depression following baseline assessment. In an older and shorter double-blind RCT of DHA monotherapy in 36 participants, erythrocyte DHA increased two-fold in individuals with major depressive disorder taking 2000 mg DHA/day while there was no change in the control group, yet there was no difference in depressive symptoms response rate between the two groups (39). The researchers speculated the treatment time of 6 weeks may have been too short, the DHA dose inadequate to elicit an effect, EPA may be more effective, or that both EPA and DHA were required (39).

Studies using combined EPA and DHA as an omega-3 monotherapy show little benefit, although this may be because of confounding factors. For example, mood improved significantly in both treatment (630 mg EPA and 850 mg DHA/day) and control (olive oil) individuals with mild to moderate depression after 12 weeks compared with baseline but the treatment group showed no significant improvement over controls (40). Although this trial had a large sample size ($n = 218$), the dose of omega-3 was modest compared with other studies. An RCT published in the same year (2003) also found no improvement in mood in men with angina who were advised to increase their fish intake or to take fish oil capsules, compared with those who were not given this advice (41). This was despite the study being much longer, at 6 months, and the sample size being much larger ($n = 377$). Although baseline fish intakes were 'low' at less than twice a week, plasma or erythrocyte omega-3 levels were not measured and it is not known whether baseline fish intake was already adequate in terms of mood effects. Further, the participants were only told to increase fish intake or to take fish oil capsules, but neither a specific quantity or type of fish was prescribed and hence the increase in fish oil consumption may not have been sufficient for a therapeutic change.

The relationship between the dose of omega-3 fatty acids and the effect on depressive symptoms may not be linear. A double-blind dose-finding study (42) in adults with major depressive disorder showed there may be a therapeutic window in that higher doses of omega-3 may attenuate antidepressant effects. After 12 weeks, 1000 mg/day DHA appeared more effective than 2000 or 4000 mg/day, although the difference was not significant. However, this trial did not have a placebo arm, leaving the potential for spontaneous remission in all three trial groups. Evidence of a therapeutic window was also shown in an earlier and larger double-blind study, where adults with depression despite standard antidepressant therapy were randomised to a liquid paraffin placebo or 1000, 2000 or 4000 mg/day ethyl-EPA as adjunctive treatment (43). At 12 weeks, there was significant improvement in symptoms from baseline in those on 1000 mg/day ethyl-EPA but only weak evidence of greater improvement in the 4000 mg/day group compared with the level of improvement in the placebo group (43).

As with bipolar disorder, there have been very few empirical studies into omega-3 fatty acids and depression in children. One small double-blind RCT showed children with major depressive disorder improved significantly on 380 mg EPA and 180 mg DHA/day compared with those taking placebos of olive oil and safflower oil after 16 weeks.

Postpartum depression and depression during pregnancy

Omega-3 fatty acids have appeal as a potential treatment for perinatal or postpartum depression, given concerns regarding the effect conventional pharmacological agents may have on foetal and maternal health (44). Women who became depressed after delivery ($n = 10$) had significantly lower plasma DHA and total omega-3 levels at delivery compared with those who did not develop depression ($n = 38$) (45). An important confounder of note in this study is the lack of dietary intake data. In a more recent study which did measure dietary fish intake, no association between the presence of depression and plasma omega-3 levels or eating or not eating fish during pregnancy in 80 first-time mothers (46). Consuming any fish at all was associated with higher EPA, DHA and total omega-3, as well as lower omega-6:omega-3 ratios, although many of those who consumed fish only ate white fish, which

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has a lower omega-3 content than oily fish and consequently may have contributed to lower mean plasma omega-3 levels (46)

Controlled and open-label trials in recent years show minimal benefit in postpartum depression. EPA and DHA monotherapy in pregnant women with major depressive disorder led to greatly reduced the magnitude of depressive symptoms in a recent open-label pilot study (44). However, it is difficult to draw conclusions as dosages were titrated according to clinical assessment and participant preference and individual trial duration ranged from 2 to 22 weeks. Therapeutic dose may not have been reached for many of the participants and there was a possibility of a strong placebo effect (44). There was also no assessment of baseline dietary intakes of fish or essential fatty acids. More recently, depression significantly improved in women with major depression or dysthymia, whether given 6000 mg/day fish oil or placebo, but there was no difference in depression scores between treatment and placebo groups in the 6-week double-blind RCT (47). This was despite significantly increased plasma omega-3 in participants taking fish oil compared with no change in the placebo group. However, the sample size was small and it was likely the women had milder levels of depression (47). An older longitudinal and placebo-controlled trial of pregnant women resulted in an 8% increase in plasma DHA in those supplemented with 200 mg/day algal DHA for 4 months following delivery and a 31% decrease in the placebo group, but no significant difference in depressive symptom severity. This suggests that DHA supplementation did not prevent the development of postpartum depression, but the generally low scores in the sample made it difficult for changes in mood to be detected (48). Llorente et al. (48) cautioned that the Beck Depression Inventory used may not be sufficiently sensitive to detect syndromal depression postpartum. This trial was criticised for not studying a vulnerable population sample (49) and the dose of DHA used was low compared with other studies discussed here.

Omega-3 fatty acids may be better as an adjunct treatment to conventional antidepressants than as a monotherapy (47). There are few studies into the use of omega-3 as an adjunct to conventional antidepressant treatment in pregnancy or during the postpartum period and this is likely to reflect ethical issues in conducting such studies. One study found that no difference in depressive symptomatology between women with perinatal major depressive disorder receiving 1100 mg EPA and 800 mg DHA/day with adjunct *psychotherapy* and those receiving only psychotherapy, after 8 weeks (50). Depression severity decreased significantly in both groups and baseline fish intake was low. Thus, omega-3 fatty acids may not provide additional benefit over psychotherapy but it is also not known if the dose was optimal or whether the duration of the trial was sufficient.

As mentioned earlier, background dietary factors may confound results. In pregnant women with major depressive disorder, 2200 mg EPA and 1200 mg DHA/day over 8 weeks commencing between 16 and 32 weeks of gestation, led to significantly greater improvement than in the placebo group in a double-blind RCT (51). The remission rate did not differ significantly between treatment and controls, but this study was conducted in Taiwan where fish consumption is high and pregnant women tended to increase their fish intake (51). Similarly, a large prospective study in Japan found no significant dose-response association between intakes of fish, omega-3, EPA, DHA or omega-3:omega-6 ratios and the risk of postpartum depression (29). However, the study reported an inverted J-shaped relationship between risk of postpartum depression and intake of omega-3 and DHA. Japanese and Western diets differ greatly and fish intake might benefit populations who have low fish consumption (29). Japanese fish consumption is substantial, with the mean dietary intake in this sample providing 1700 mg alpha-linolenic acid, 200 and 300 mg DHA/day. Other environmental factors warrant mention, as high fish intake also provides the potential for other agents such as dioxins and methylmercury to mitigate otherwise beneficial effects (29). The potential detrimental effects of mercury contaminants in seafood were also raised by Sanchez-Villegas et al. (11).

As with depression and bipolar disorder, the dose of omega-3 fatty acids may be critical to the level of therapeutic impact. An 8-week pilot RCT of women in their third trimester and at high risk for postpartum depression found no advantage to more than 500 mg/day omega-3 fatty acids (52). All groups improved significantly from baseline, whether on 500, 1400 or 2800 mg omega-3/day. Baseline fish intake was low and there was no difference across the groups in symptom severity either at baseline or post-treatment. As there was no control group, a placebo response is highly possible.

Attention deficit hyperactivity disorder and behaviour problems

Most nutritional studies in this area have focused on ADHD and there are few empirical studies into nutrition and conduct disorder or learning disorders. A recent longitudinal study found lower DHA status at birth was associated with childhood 'internal' problem behaviours such as anxiety, depression,

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somatic complaints and withdrawn behaviour at age 7 (53). However, this DHA status was not associated with 'external' problem behaviours such as aggression and rule breaking. Further, levels of long-chain polyunsaturated fatty acids at age 7 were not associated with problem behaviours. There were limitations to this longitudinal study, including the use of parental reports rather than an object measure of behaviour, and confounding by environmental factors such as parenting styles and parental psychopathology (53). Nevertheless, the study is an example of 'early programming' for later disease.

Individuals with ADHD may have higher omega-3 requirements. Lower plasma levels of essential fatty acids are associated with ADHD and increased behaviour problems (54). A small cross-sectional study found adolescents with ADHD had lower levels of total omega-3 fatty acid, lower DHA and lower omega-3:omega-6 ratios in their erythrocyte membranes than controls, even though their dietary alpha-linolenic acid, DHA and EPA and omega-3:omega-6 ratios were similar (55). Also, erythrocyte DHA content negatively correlated with oppositional behaviour, hyperactivity, restlessness and inattention. Those with ADHD had significantly higher energy and macronutrient intakes and higher total fat, saturated fat and trans-fat intakes, with the total and saturated fat positively correlating with oppositional, hyperactive and problematic behaviours. However, the ADHD group had lower body fat mass and percentage body fat mass than controls (55), suggesting individuals with ADHD may have higher energy requirements.

Metabolism of essential fatty acids may be less efficient in individuals with ADHD. Chen et al. (56) speculated that children with ADHD have a lower capacity to convert 18-carbon chain fatty acids–linoleic and alpha-linolenic acids–to longer chain polyunsaturated fatty acids. Their study found no difference in dietary intakes of linoleic, alpha-linolenic, oleic (omega-9) or saturated fatty acids, nor a difference in energy, protein, total fat or carbohydrate intakes between children with and without ADHD, yet the erythrocyte membranes of children with ADHD were significantly lower in alpha-linolenic acid, arachidonic acid, DHA, total omega-3 and omega-3:omega-6 ratios. As erythrocyte alpha-linolenic acid levels were lower in ADHD individuals compared with controls, despite similar dietary intakes, it is possible children with ADHD have difficulties absorbing, transporting or storing this essential fatty acid.

Open-label trials have generally shown improvements in ADHD symptoms. Inattention and hyperactivity levels significantly improved on supplementing children with ADHD with fish oil (2500 mg/10 kg body weight/day) for 8 weeks and showed significant reductions in arachidonic acid:EPA ratios in erythrocyte membranes (57). Similarly, significant improvement in inattention, hyperactivity, oppositional/defiant behaviour and conduct disorder and increases in plasma phospholipids EPA and DHA was observed in a small 8-week pilot study (58). Another open-label trial which used 400 mg flax oil and 50 mg/day vitamin C significantly improved ADHD symptoms in 30 children with ADHD who were not taking stimulant medication, after 3 months (59). The flax oil also significantly decreased erythrocyte membrane arachidonic acid and increased EPA and DHA (59). None of these studies assessed dietary intake or controlled for it during the trial, and it is not known what contribution diet made to the plasma phospholipids profile. The open-label design of these trials also leaves them vulnerable to the placebo effect.

Supplementing Australian children with ADHD combination of fish and evening primrose oils (a source of the omega-6 fatty acid gamma-linolenic acid) significantly improved Conners ADHD and Global Index scores, as well as hyperactivity, impulsiveness, oppositional behaviour and restlessness, compared with a placebo of palm oil over 15 weeks (60). This was a large RCT with 104 participants and included a group supplemented with both fish and evening primrose oils and multivitamins and minerals. The trial continued for a further 15 weeks in which all three groups consumed fish and evening primrose oils and multivitamins and minerals. The former placebo group significantly improved from their status at week 15 while those already taking fish and evening primrose oils showed continued improvement on the Conners ADHD and Global Indices, restlessness, impulsiveness and hyperactivity (60). Micronutrient supplementation did not confer benefits above those seen with essential fatty acids. However, there were no baseline assessments to determine if any of the participants were deficient in either essential fatty acids or in micronutrients, and the participants who dropped out of the trial tended to have more severe symptoms which warranted medication (an exclusion criterion) or reduced their compliance to the study's protocol. Nevertheless, in contrast to medication which is not known to provide benefits beyond 4 weeks, fish and evening primrose oils led to continuing improvement even after 15 weeks of treatment (60).

Older, smaller RCTs had mixed findings. There was a general lack of benefit of a mixture of long-chain omega-3 and omega-6 fatty acids (480 mg DHA, 80 mg EPA, 40 mg arachidonic acid and 96 mg gamma-linolenic acid) on symptoms at the end of a 4-month controlled pilot study of 50

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children with ADHD and signs of essential fatty acid deficiency, even though erythrocyte membrane content of EPA and DHA increased greatly (61). This study assessed 3-day diet records both at the start and end of the intervention but did not use them in their analyses. In contrast, ADHD symptoms significantly improved with supplementing children with omega-6 and omega-3 fatty acids (186 mg EPA, 480 mg DHA, 96 mg gamma-linolenic acid, 864 mg linoleic acid and 42 mg arachidonic acid) over a 12-week pilot study (62). A major limitation was that none of the 41 participating children had ever been formally diagnosed with ADHD and the fatty acid profiles of plasma or erythrocyte membranes were not assessed. A slightly larger study of 54 children with ADHD significantly increased plasma DHA and decreased EPA and arachidonic acid after supplementation with 345 mg DHA/day for 4 months in a RCT (63). There was no difference between treatment and control groups in their mean Child Behaviour Checklist and Conners' Rating Scale scores at baseline or at 4 months (63). The general lack of effect of DHA supplementation may mean children need a longer period of supplementation or a higher DHA dose (63). Also, as the children continued their medication during the study, DHA may not be effective as an adjunct treatment. Background dietary intakes of omega-3 were not controlled for in the latter two studies.

Studies in ADHD and omega-3 focus mainly on children and have generally shown some beneficial effects but only a few studies have investigated adults, making it premature to draw conclusions in this age group. In adults, one study observed no association between ADHD symptom severity and serum or erythrocyte membrane DHA levels, but alcohol and tobacco use were not controlled for and it could not be determined whether diet contributed to the fatty acid profile (64). However, those with ADHD had significantly lower erythrocyte omega-3 and DHA and their serum phospholipid levels of DHA, docosapentaenoic acid (omega-3) and omega-6 fatty acids were also lower, although the participants were not fasting when blood samples were taken (64). An RCT comparing olive oil, flax oil and fish oil in adults with ADHD focused on the ability of these oils to alter serum phospholipid profiles, but unfortunately did not investigate if the treatments altered ADHD symptoms (65). In a much older trial, fish oil did not change levels of aggression in healthy young adults towards others after 13 weeks, but those taking a placebo of soybean oil had significantly decreased aggression (66). Hostility levels did not change in either group. However, this was a Japanese study and although dietary data was not presented, fish intake is generally high in the Japanese population. It was also unclear if the levels of aggression measured were of clinical or pathological importance.

Interpretation of trials using omega-3 preparations have generally been hampered mostly by their small sample sizes and by placebos which may themselves influence mood (8). The choice of placebo is important in RCTs as many oils are not biologically inert. Olive oil is a commonly used placebo (20,22,34,35,40,61) and is a source of linoleic acid, an omega-6 fatty acid and precursor of arachidonic acid. Also, olive oil is rich in oleic acid, which is metabolised to psychoactive oleamide (62). Soybean and rapeseed oils have also been used as placebos (66,67), both of which have substantial linoleic (omega-6) fatty acid contents and rapeseed oil also being a source of alpha-linolenic acid. Sunola oil (47) is also a source of linoleic acid and corn oil has a substantial linoleic acid content (50,52). It is also not clear what bioactive potential olive oil esters, used as placebo in a number of studies (17,36,51), may have in mood and behaviour. Further, some studies do not detail what placebo was used (37,38,42,48,68,69). The choice of carrier is also important: one study acknowledged the use of foods as a vehicle for the oils was not ideal as blinding was compromised (67). It is also possible that the active component in seafood may not be DHA or EPA. In addition, baseline dietary intakes are not always assessed, sometimes they are assessed but not adjusted for in the analyses and diets consumed throughout trials are often not controlled.

Apart from the role of essential fatty acids, a British pilot study reported that a diet with lower overall fat content than recommended was associated with increased anger-hostility and depression in healthy adults (70). However, a very low fat diet, in this case, only 25% of calories, is unpalatable to many people and the possibility of this itself having an adverse effect on mood was not explored by the authors.

Dietary protein and carbohydrate

The literature regarding the effects of protein and carbohydrate on mood and behaviour is much older than that on omega-3 fatty acids, with empirical research mostly published in the 1970s to 1980s. The proportion of carbohydrate and protein in the diet can, in theory, influence mood by modifying tryptophan, a precursor to serotonin, uptake by the brain. The widely quoted Wurtman hypothesis states that a carbohydrate-rich meal stimulates the release of insulin, causing most of the amino acids other than tryptophan to be taken up by the peripheral tissues.

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The resulting higher ratio of tryptophan to large neutral amino acids leads to proportionately more tryptophan being transported into the brain (71–73). However, a mere 5% of calories as protein is sufficient to circumvent the Wurtman effect and most foods considered high in carbohydrate will still contain enough protein to prevent the Wurtman effect occurring (72). Also, it is not certain if plasma amino acid ratios translate to ratios in the brain in humans (74).

Very few studies have used the Wurtman hypothesis in an attempt to modify mood. Plasma tryptophan to large neutral amino acid ratios can be elevated significantly by administering high carbohydrate-low protein diets (75). In individuals deemed highly prone to stress, high protein-low carbohydrate diets increased depression when stress was induced. However, in individuals less prone to stress, both high carbohydrate-low protein and low carbohydrate-high protein diets led to increased depression. Baseline plasma amino acid ratios were not measured, so it is not known if the test diets altered fasting amino acid profiles. Further, as the diets were administered on the test day only, the findings only represent acute effects. A decade earlier, a study into weight loss diets found low tryptophan to large neutral amino acid plasma ratios were associated with worse mood, but as the participants were free-living and advised only on maintaining a 'mixed' or a 'vegetarian' diet, protein and carbohydrate intake were not controlled (76). Factors other than diet composition, and its metabolic consequences, may influence mood. One example is diet palatability (77). It is unlikely that the highly artificial dietary regimes needed to achieve such effects would be consumed in the community. Other studies have used more direct means to elevate plasma tryptophan, such as supplementation to alter amino acid ratios (78–80). The results of these studies have been inconsistent and healthy young individuals also may be less susceptible to such dietary manipulations and supplementation (78).

One other aspect of carbohydrate deserves mention, namely refined sugar. There are strong parental beliefs that sugar intake increases hyperactivity in children (54). Published empirical research into the effects of refined sugar on mood and behaviour is quite old. Studies in the 1970s which supported increased hyperactive behaviour in children, when sucrose was initially removed and then returned to the diet, usually did not include a control group or use double-blind methodology (81). Also, removing sugar greatly changes a diet's overall composition (73). In young adults, ingestion of a 100 g load of sucrose was not associated with a difference in mood compared to a fasting state except for less anxiety after 4 h and additionally, saccharin and water did not elicit changes in mood compared to fasting (82), although serum glucose levels were not measured. Some studies used an inappropriate placebo. For example, a study comparing different sugar solutions used orange juice as a control, which in itself contains simple sugars, and found no differences in the behaviour of children who had been hospitalised for anxiety, attention deficit and severe behaviour disorders (83).

Most controlled studies do not support sucrose promoting hyperactivity, even in children diagnosed with attention deficit disorder (81,84,85), and some studies reveal a decrease in activity levels after ingesting sucrose or glucose (73,81). Parental expectations of the effects of refined sugar on children's behaviour are also pertinent (86). There is an additional caveat that very active children will have greater energy requirements than their sedentary counterparts and high sugar intakes would contribute to their requirements (81). Curiously, Benton's review (87) noted purported adverse effects of a high sugar intake in children but potential adverse effects of *low* blood sugar on aggressive behaviour in adults. In the case of adults, Benton (87) speculated that it may not be the propensity for developing low blood glucose which directly influences violent behaviour, but that low blood glucose is an indicator for low brain serotonin. Nevertheless, refined or added sugar can be removed from children's diets with little detriment or cost (54) and removal has other potential nutritional benefits in relation to obesity and dental caries.

Food additives

Recent reviewers observed a lack of scientific evidence for the efficacy of the Feingold diet, a diet devoid of salicylates, artificial food colourings and artificial flavourings, in treating ADHD (54,81,88). Schab and Trinh's meta-analysis (89) in 2004, of 15 trials using artificial food colours and flavours in hyperactivity, highlighted the heterogeneity of such studies in terms of dosage and types of colours and flavours used, whether the children had a rigorous ADHD diagnosis, and the adequacy of the various washout periods used in the cross-over studies. The meta-analysis was unable to verify whether children rigorously diagnosed with hyperactivity were more susceptible to the effects of the colours and flavours compared with children with informal or no diagnoses. However, Schab and Trinh (89) still reported a strong suggestion of an association between the colours and flavours and hyperactivity.

Earlier studies had methodological problems. One study of 3–12 year olds who met Diagnostic and

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Statistical Manual of Mental Disorders (DSM) III criteria for attention deficit disorder with hyperactivity (90) screened for children whose symptoms improved on a limited foods diet and then subsequently enrolled them in a double-blind cross-over RCT. There was a significant difference in the children's behaviour as rated by the psychologists, but it is not clear if the magnitude of difference is of clinical importance. However, the limited foods diet used for screening the children still included a variety of foods which contained potentially provoking compounds and so was not as stringent as an elimination diet. For example, the diet contained vegetables which were not described and which may have contained salicylates, and banana which is rich in amines, another potentially aggravating group of compounds. Further, in the double-blind phase, the foods used as carriers to disguise the trial foods also contained provoking compounds themselves, such as chocolate (amines), pineapple juice (both amines and salicylates) and apricot juice (salicylates) (91).

Studies conducted in the past 5 years have been much better designed, but still have problems. McCann et al.'s recent double-blind RCT of a mixture of artificial food colours and the preservative sodium benzoate in 3-year-old and 8- to 9-year-old children in the community resulted in increased hyperactivity levels (92). The quantities administered were the equivalent of additives, which would be present in 112–224 g confectionary per day. As a mixture of additives was tested, it is not known which one(s) were responsible for the increased hyperactivity or whether the additives were synergistic in their effects. The children's baseline intakes of these additives were not assessed, nor were the children's diets controlled throughout the trial and there was considerable variability in the children's responses (92,93). A slightly older double-blind controlled trial used similar quantities of artificial colours and preservatives but with a background diet free of the same additives and found no difference between treatment and placebo using objective tests (94). However, hyperactivity significantly increased according to parental ratings during both placebo and treatment phases. This trial has been criticised for its study sample's prevalence of hyperactivity, which was higher than in the community, and as it was a trial in 3 year olds, a diagnosis of ADHD could only be provisional (95).

In practice, it can be argued that the amount of confectionary represented by McCann's trial would, on a regular basis, replace other more nutritious foods in children's diets. While artificial food colours and flavours may be considered extraneous in children's diets, sodium benzoate has an important role in food safety as a preservative (92). The removal of artificial food colours, flavours and preservatives from children's food could be of considerable public health benefit (88), but the restrictiveness of a diet free from artificial colours and flavours is a potential burden itself on hyperactive children. It is not known whether the dietary mechanism is toxicity, pharmacological or allergic, and it could not be concluded that dietary treatment was useful for all children with hyperactivity. A diet free of artificial food additives should not be implemented routinely until further methods to identify responsiveness to these substances have been developed (89) and there is a little rationale for assuming that every additive in the Western diet is detrimental (87).

Micronutrients

Numerous nutrients are hypothesised to affect mood and behaviour. While there has been reasonable research into micronutrients and behaviour, there has been much less empirical research into mood. For example, Benton's (87) review focused on nutrition and violent and aggressive behaviour in adults and children rather than mood and did not discuss which of the various micronutrients were critical to behaviour.

Specific vitamin deficiencies result in classic symptoms and clinical pictures. For example, there is good evidence that thiamine deficiency is associated with low mood and some evidence that thiamine supplementation improves mood in individuals with adequate thiamine status, although it is not clear in the latter whether this is a physiological or pharmacological effect (72). Pellagra (niacin deficiency) is an example of a vitamin deficiency which results in psychiatric symptoms (73). Low levels of folate and vitamin B6 may also be associated with depressive symptoms. Oxidative stress is associated with bipolar disorder and depression; depression itself may be a chronic inflammatory condition and major depression is possibly associated with flawed antioxidant defences (1,96,97). Low vitamin E may be associated with depression, as vitamin E is an antioxidant, although no intervention studies have been done in this area (97).

Mood disorders may result from latent long-term deficiencies, or it may be that long-term psychological stress alters the absorption of nutrients and thus influences brain development (97). Supplementing healthy young adults with a multivitamin in a year-long double-blind RCT resulted in improved self-reported mental health in women, but not men (98). In particular, better serum levels of riboflavin and vitamin B6 were associated with improved mood in women. The gender difference

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could not be explained, but a comparison between men and women's baseline vitamin status was not reported (98). More recently, a cross-sectional study of Japanese adults living in the community found men with depressive symptoms were significantly more likely to have lower dietary intakes of folate, but this was not observed in women (28). Also in men, those in the second quartile for vitamin B12 intake had significantly lower prevalence of depressive symptoms than those in the first quartile (28).

Among minerals, iron deficiency without anaemia is associated with feelings of depression in individuals taking oral contraceptives (72). Iron supplementation in adolescent girls resulted in a significantly greater proportion reporting improvement in lassitude, concentration and mood compared with the placebo group in a double-blind RCT (99). Of those who improved, the majority had commenced the trial with hypoferremia and became normoferremic at the end of the supplementation period. Selenium deficiency may adversely impact on mood and anxiety, but studies which investigated selenium supplementation and selenium depletion highlighted the crudity of the methods used to ascertain individuals' dietary intakes of selenium, the duration of time needed appreciably to alter selenium levels in the central nervous system and the potential toxicity of excess selenium (100,101). Other minerals associated with depression include low calcium, magnesium and zinc (97).

There have been a number of empirical studies into behavioural disturbances and micronutrients in the past 5 years. Recently, iron intake was found to *positively* correlate with inattentiveness, cognitive problems, problematic behaviours, restlessness, oppositional, hyperactivity and ADHD scores in adolescents, in a case-control study (55). Intakes of iron, thiamine and riboflavin were also significantly higher in those with ADHD. An earlier study also observed ADHD children had significantly higher dietary intakes of iron as well as vitamin C and significantly higher serum iron than children without ADHD, and that neither group were deficient in iron (56). This may reflect larger overall nutritional intake in individuals with ADHD, as energy, protein, carbohydrate were higher in both studies (55,56) and significantly higher in Colter's sample (55). However, in intervention studies, there was increased lipid peroxidation in ADHD children following supplementation with flax oil, despite supplementing with vitamin C as an antioxidant, and ADHD symptoms significantly improved in this open-label trial (59). Higher levels of antioxidants may be needed to reduce peroxidation (59). The addition of a multivitamin and minerals in the large RCT discussed earlier neither gives additional benefits nor attenuates the effects of omega-3 in treating ADHD symptoms in children (60). In contrast, an older small double-blind RCT of zinc sulfate as an adjunct to methylphenidate in children led to significantly improved ADHD symptoms after 6 weeks when compared to methylphenidate alone (102). These three studies did not assess for baseline micronutrient deficiencies (59,60,102); it is also possible that a clinical population may need higher intakes than that provided by the intervention (60). An intervention study a decade earlier found correcting blood nutrient deficiencies is associated with improvements in antisocial behaviour, including violent behaviour, in adolescent inmates (103).

Kaplan et al. (97) stated that there have been too few controlled trials in micronutrients to merit a meta-analysis. There are also a number of practical issues in measuring micronutrient status and translating it to the effects on the brain. These include: that cerebrospinal fluid levels do not necessarily indicate that the brain has sufficient nutrients for optimal function; that plasma or serum levels of nutrients often reflect recent intake rather than actual nutritional status; and that even reliable serum indicators of long-term micronutrient status may not reflect the level of micronutrients in the brain. An association does not imply cause and effect, as low micronutrient intake may result from depressive symptoms promoting poor dietary intake as well as inadequacies in other health behaviours (97). This is also true of studies on fish and omega-3 fatty acid intakes (104). Further, 'adequate' dietary intake may not translate to adequate physiological tissue levels, particularly in disease states.

Conclusion

Research into mood, behaviour and diet has mostly focused on depression and ADHD. Much of the research has been undertaken in adults, although research into ADHD has focused predominantly on children. There are promising pilot data showing the potential for omega-3 fatty acids in helping to manage mood disorders and ADHD, which warrant further research. Overall, long-chain omega-3 fatty acids may benefit those who have low intakes of fish and seafood and who have more severe levels of depression, but it is presently unclear what dose or ratio of EPA to DHA would be optimal. Current studies of omega-3 as a treatment in postpartum depression show minimal benefit.

Some dietary treatments, such as manipulating tryptophan levels through carbohydrate and protein intakes, are unsuitable for using outside the laboratory, owing to the highly artificial and impractical

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diets required. While public beliefs regarding the role of refined sugar and food additives in hyperactivity in children are strong, empirical evidence for the role of sugar is lacking and for food additives, dosage and individual sensitivity should be examined before imposing a restrictive diet on a child. Nevertheless, the lack of evidence for an association between sugar and hyperactivity should not be taken that sugar should be consumed ad libitum. Refined sugar has been termed 'empty calories' in that it contributes energy without other nutrients. A high intake of refined sugar may well replace more nutritious foods in an individual's diet, which would be detrimental to overall health, including dental health and in terms of obesity and its associated metabolic comorbidities. Research into the effects of micronutrients on mood is somewhat old but shows micronutrient deficiency is associated with low mood with little evidence to support improved mood by supplementing replete individuals with micronutrients. There have been more studies into micronutrients and behaviour in recent years but design issues make results inconclusive.

There are various common methodological limitations to the studies undertaken so far and more recent studies are not necessarily better designed than older ones. Many were cross-sectional and it can be argued that poor mood or mental status is the cause of poor diet, and studies without placebo groups require cautious interpretation. In numerous studies into essential fatty acids where placebos *were* used, the materials were often biologically active and thus may confound results. Many studies do not assess for the presence of baseline nutrient deficiencies and a lack of effect may be because of individuals being nutritionally replete overall. Longitudinal studies are warranted, as are studies into therapeutic windows and intervention studies with adequate duration, larger study samples, double-blind methodology, controlling dietary intake throughout a trial and using biologically inert placebos. The background contribution of dietary intake of the various nutrients should also be routinely taken into account, as should physiological status, such as appropriate serum or tissue indices.

It should be emphasised that even if the effects of diet do not produce direct and clinically meaningful benefits for particular psychiatric disorders, a nutritionally adequate diet and good nutritional status, together with increased physical activity, are still important for an individual's overall health (1,105). However, should the effectiveness of omega-3 fatty acid supplementation or the elimination of certain food additives be substantiated, they may prove to be cost-effective, accessible and well-tolerated adjuncts to standard psychiatric treatments.

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