2016

People with schizophrenia and depression have a low omega-3 index

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Publication Details

Parletta, N., Zarnowiecki, D., Cho, J., Wilson, A., Procter, N., Gordon, A., Bogomolova, S., O'Dea, K., Strachan, J., Ballestrin, M., Champion, A. & Meyer, B. J. (2016). People with schizophrenia and depression have a low omega-3 index. Prostaglandins, Leukotrienes and Essential Fatty Acids, 110 42-47.

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Abstract
Cardiovascular disease (CVD) is higher in people with mental illness and is associated with a 30 year higher mortality rate in this population. Erythrocyte docosahexaenoic acid (DHA) plus eicosapentaenoic acid (EPA) (omega-3 index)≤4% is a marker for increased mortality risk from CVD while >8% is protective. Omega-3 polyunsaturated fatty acids are also important for brain function and may ameliorate symptoms of mental illness. We investigated the erythrocyte omega-3 index in people with mental illness. One hundred and thirty adults aged 18-65 years (32.6% male) with schizophrenia (n=14) and depression (n=116) provided blood samples and completed physiological assessments and questionnaires. Both populations had risk factors for metabolic syndrome and CVD. The average omega-3 index was 3.95% (SD=1.06), compared to an estimated 5% in the Australian population. These data indicate an unfavourable omega-3 profile in people with mental illness that could contribute to higher CVD risk.

Disciplines
Medicine and Health Sciences | Social and Behavioral Sciences

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People with schizophrenia and depression have a low omega-3 index

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ABSTRACT *(max 150 words)*

Cardiovascular disease (CVD) is higher in people with mental illness and is associated with a 30 year higher mortality rate in this population. Erythrocyte docosahexaenoic acid (DHA) plus eicosapentaenoic acid (EPA) (omega-3 index) ≤ 4% is a marker for increased mortality risk from CVD while >8% is protective. Omega-3 polyunsaturated fatty acids are also important for brain function and may ameliorate symptoms of mental illness. We investigated the erythrocyte omega-3 index in people with mental illness. One hundred and thirty adults aged 18-65 years (32.6% male) with schizophrenia (n=14) and depression (n=116) provided blood samples and completed physiological assessments and questionnaires. Both populations had risk factors for metabolic syndrome and CVD. The average omega-3 index was 3.95% (SD=1.06), compared to an estimated 5% in the Australian population. These data indicate an unfavourable omega-3 profile in people with mental illness that could contribute to higher CVD risk.

Keywords: polyunsaturated fatty acids, omega-3, omega-3 index, mental illness, depression, schizophrenia, cardiovascular disease

INTRODUCTION

In 2001 the World Health Organisation reported that around 450 million people worldwide suffered from a mental health problem and that one in four people will experience mental illness at some stage in their life [1]. Recent findings from the World Health Organisation's World Mental Health survey identified that mental disorders are common across 28 participating countries, with an interquartile range from 18.1-36.1 per cent of lifetime prevalence [2]. Like physical health, mental health is a complex interaction of biological, psychological and social factors [1]. Not only does chronic mental illness lead to substantially reduced quality of life, social and economic burden, it is compounded by high rates of physical illness. People with serious mental illness (SMI) are more likely to suffer from a range of physical health problems, particularly metabolic syndrome/diabetes and cardiovascular disease (CVD) [3-6]. Behavioural factors that lead to poor lifestyle choices such as smoking, diet and low physical activity contribute to this higher risk [1, 7]. Although medications also contribute to CVD risk factors, lifestyle factors such as poor diet (e.g. low fibre, high fat, high sugar) have been identified as independent contributors [8-10].

These lifestyle behaviours may contribute to common underlying biological mechanisms for both physical and mental illness and their comorbidities [11]. Supporting evidence comes from a meta-analysis of epidemiological studies showing a significant association between depression and metabolic syndrome [6], a cluster of risk factors for CVD including hyperglycemia and/or insulin resistance, hypertension, abdominal adiposity and hyperlipidemia. Interestingly, prospective studies identified in the latter review showed that the association is bidirectional. Another meta-analysis showed that depressed adults have a 37% increased risk of developing diabetes [5]. These studies provide evidence that people don't develop depression as a result of being physical ill, and that in fact there may be

underlying mechanisms that manifest as mental illness before symptoms of physical illness become apparent.

One of the possible common contributors to both cardiometabolic and mental health is the group of omega-3 long chain polyunsaturated fatty acids (n-3 LCPUFAs). The benefits of n-3 LCPUFA for cardiovascular health have been well established [12] (despite recent studies which are plagued by methodological issues, largely associated with the fact that they were conducted after 2000 and 2002 American Heart Foundation recommendations for increased fish and fish oil intake respectively, and subsequent exponential increase in fish oil imports [13, 14]). Mechanisms for reducing CVD risk may include reduction of ventricular arrhythmia, thrombosis, triglycerides, atherosclerotic plaque, inflammation and hypertension, and endothelial relaxation [15]. Based on the body of evidence, an omega-3 index for cardiovascular health was developed by Harris and von Schacky [16]. They first established erythrocyte levels of the long chain n-3 LCPUFAs eicosapentaenoic acid (EPA; 20:5n-3) plus docosahexaenoic acid (DHA; 22:6n-3) as a valid biomarker of omega-3 status. Then by pooling together results from a body of large prospective and randomised controlled trials they identified that a combination of EPA plus DHA levels of $\leq 4\%$ in erythrocyte membranes was associated with the highest risk of mortality from coronary heart disease (CHD) whereas levels $\geq 8\%$ conferred the greatest cardioprotection. Therefore the omega-3 index was proposed as a useful biomarker to estimate risk of mortality from CHD and provide targets for reducing mortality risk.

Since the prevalence of n-3 LCPUFA DHA in brain tissue was discovered in the 1970s [17] a number of pivotal roles have been identified for DHA in brain function, including a key structural role in brain cells and phospholipids, neurite growth, membrane fluidity,

neurotransmission (e.g. synthesis of neurotransmitters serotonin and dopamine), endothelial function and brain barrier integrity, neuronal survival and protection from neurodegeneration [18]. The role of EPA and DHA in improving endothelial function via production of anti-inflammatory eicosanoids, reducing adhesion of substances to the endothelial wall and influence on nitric oxide production (and therefore vasodilation and blood flow) may contribute to common underlying mechanisms for their protective role in cardiovascular and mental health [19]. A growing body of work has investigated the role of n-3 LCPUFAs in mental health with indications of benefit across the lifespan including developmental disorders, depression, schizophrenia and cognitive decline [20, 21]. Following the latter studies reviewed, a robust multi-centre trial reported that n-3 LCPUFA supplementation for 12 weeks was able to significantly reduce transition to psychosis at 12 month follow-up compared to placebo in young people at high risk for psychosis [22]. We previously proposed an omega-3 index for mental health although there were as yet insufficient blood fatty acid data to establish this [23].

Inflammation has been proposed as a possible mediating role for comorbid physical and mental illness [24-28] and may be one of the mechanisms by which n-3 PUFA exert their effects. The anti-inflammatory properties of eicosanoids produced by EPA counteract the largely inflammatory properties of eicosanoids produced by arachidonic acid (AA) from the n-6 PUFA series. The n-3 and n-6 PUFA series compete for the same enzymes for elongation and desaturation, and a higher intake of one can displace the other in cell membranes. This is of concern in Western societies that have increased the intake of n-6 PUFA via vegetable oils and processed foods while decreasing intake of n-3 PUFA from nuts, seeds, dark leafy vegetables and fatty fish, including Australia [29, 30]. It has been proposed therefore that the ratio of n-6/n-3 PUFAs, which in Western diets is estimated at 15-16/1 (8/1 in Australia [30])

compared to an equal ratio in traditional diets, contributes to pro-inflammatory states that underlie chronic illness [31].

In the present study we investigated erythrocyte PUFA levels in people with SMI to determine their erythrocyte omega-3 index and associations with physical and mental health. This study utilised baseline data from two related studies: a pilot study with residents of a Community Rehabilitation Centre for people with serious mental illness and a randomised controlled trial with community dwelling people suffering from depression.

METHOD

Study 1 was a partnership between the University of South Australia and the Mental Health Directorate in the Southern Adelaide Local Health Network. Ethics approval was obtained from the Southern Adelaide Clinical Human Research Ethics Committee (HREC) and the HREC at the University of South Australia. For study 2 community dwelling adults suffering depressive symptoms were recruited, for which ethics approval was provided by the HREC at the University of South Australia. Both studies aimed to investigate the effect of a Mediterranean-style diet and fish oil supplementation on cardiometabolic and mental health (HELFIMED: Healthy Eating for Life with a Mediterranean-style Diet), the first as a pilot feasibility study [32] and the second as a randomised controlled trial [33]. This report utilises baseline data from those studies. For study 1 information sessions were conducted to explain the project to staff and residents of a Community Rehabilitation Centre (CRC) with 20 beds for people with serious mental illness. The population is transient with an average stay of around 9 months. Ongoing recruitment was undertaken for the pilot feasibility study from May 2013 to February 2014 and was open to all new residents entering the CRC during that time. All consenting residents were eligible to take part. For study 2 we recruited community

dwelling people via newspaper advertisements, media releases, social media and a recruitment agency. Inclusion criteria were depressive symptoms over the past 3 months or more, age between 18-65, poor diet according to an adapted dietary screening tool and not consuming fish oil supplements over the past 3 months.

Participants

Over an 8-month period, 25 CRC residents aged 18-59 years with schizophrenia signed up for study 1 and completed baseline assessments. In the first batch of blood samples many were oxidised due to an inappropriate protocol for washing of the red blood cells which was then rectified. Therefore, 14 blood samples were available for analysis of erythrocyte fatty acids. In study 2, 164 participants aged 18-65 completed baseline assessments. Of those, 116 people had either diagnosed depression (n=75; 58%) and/or depressive symptoms in the 'severe' or 'extremely severe' range on the Depression, Anxiety, Stress scale (DASS-21) [34] and are included in these analyses. Summary characteristics are provided in Table 1.

Assessments

Baseline assessments included fasted blood samples, weight, height, waist circumference and blood pressure, and the following questionnaires: the Assessment of Quality of Life (AQoL)-8D scale [35] in both studies and the DASS-21 [34] and Positive and Negative Affect Scale (PANAS) in study 2. These are described below. A background questionnaire measured the following potential covariates: age, gender, socio-economic status (Socio-Economic Indexes for Areas decile), education level (1=completed primary school; 8=postgraduate degree), household income, physical activity (calculated as total minutes per week), smoking status (1=never smoked; 5=smoke daily), and frequency of consuming >2 alcoholic drinks per day (1=never/rarely; 5=daily).

Fatty acids

Fasted blood samples were collected by trained phlebotomists in 6ml EDTA tubes. Red blood cells were separated from plasma by low speed centrifugation and packed red blood cells were stored in 1ml micro tubes at -80C until analysis. Erythrocyte samples were thawed and prepared for fatty acid analysis according to Swierk et al [36] using the direct transesterification procedure according to Lepage and Roy [37]. Samples were analysed by flame-ionisation gas chromatography (model GC-17A, Shimadzu) using a 50m x 0.25mm internal diameter capillary column. One microlitre of the sample was auto-injected into the column, and individual fatty acids were quantified using the Shimadzu analysis software (Class-VP 7.2.1 SP1, USA). Fatty acid peaks were identified by comparison with known fatty acid standards and quantitated by comparison to the 21:0 internal standard (Nu-chek and Sigma). Erythrocyte EPA plus DHA as a percent of cell membranes was calculated to obtain the omega-3 index as reported by Harris and von Schacky [16].

AQoL-8d

The AQoL-8d is a 35-item questionnaire that is used to measure quality of life. The 35 items load onto eight dimensions, of which three represent physical domains of quality of life (independent living, pain and senses) and five represent psychological domains (happiness, self-worth, coping, relationships, mental health). These load onto two super dimensions (physical and psycho-social). The scores from each dimension are combined to create a final AQoL-8D utilities score for use in economic evaluation studies. The AQoL-8D has good validity and internal consistency with alpha coefficients of 0.89-0.96 [38].

DASS-21

The DASS is a 21-item self-report scale which provides a measure of the level of negative emotional states of depression, anxiety and stress. It is a highly reliable measure that shows high convergent validity and has good internal consistency with a Cronbach alpha of 0.82-0.93 [34, 39] Ronk et al. 2013). DASS-21 sub-scale severity ratings are calculated based on the full DASS-42 severity rating [40]. The scale was multiplied by two and divided into the severity categories to yield equivalent scores ranging from 1-5. Those with severity ratings of 4 and 5 (severe and extremely severe; study 2) are included in this study.

PANAS

The PANAS is a 20-item scale measuring positive and negative emotions. It has been validated and demonstrates reliable psychometric properties, discriminant, convergent and constructed validity. The reliability (internal consistency) of the PANAS positive and negative emotions scales were determined to be α =.89 and .85 respectively [41].

Statistical analysis

Descriptive statistics were used to identify the omega-3 index, demographic, cardiovascular and mental health parameters. Pearson correlations were used to investigate bivariate associations between the omega-3 index, mental and cardiometabolic health outcome measures. For any significant associations between the omega-3 index and physical or mental health, potential covariates that were significantly associated with outcome variables were planned to be entered into regression analyses to control for these. Significance for correlations was set at $P < 0.01$ to allow for multiple comparisons.

RESULTS

As can be seen in Table 1, average data for each sample show that both samples had CVD risk factors with BMI in the obese range, central adiposity, elevated blood pressure for participants in study 2 and slightly elevated fasting glucose in the study 1 sample. The average omega-3 index for the whole sample was 3.95% (SD = 1.06) of erythrocyte membranes. The majority (56%) of participants had an omega-3 index in the high risk range ≤ 4%, and the remaining 44% in the medium risk range from 4-8% (with only 6 participants or 4.6% with an omega-3 index > 6%). No participants had an omega-3 index ≥ 8%, the range that confers highest protection against mortality from CVD. Participant data are broken down by group in Table 1 and the distribution of the omega-3 index is shown in Figure 1.

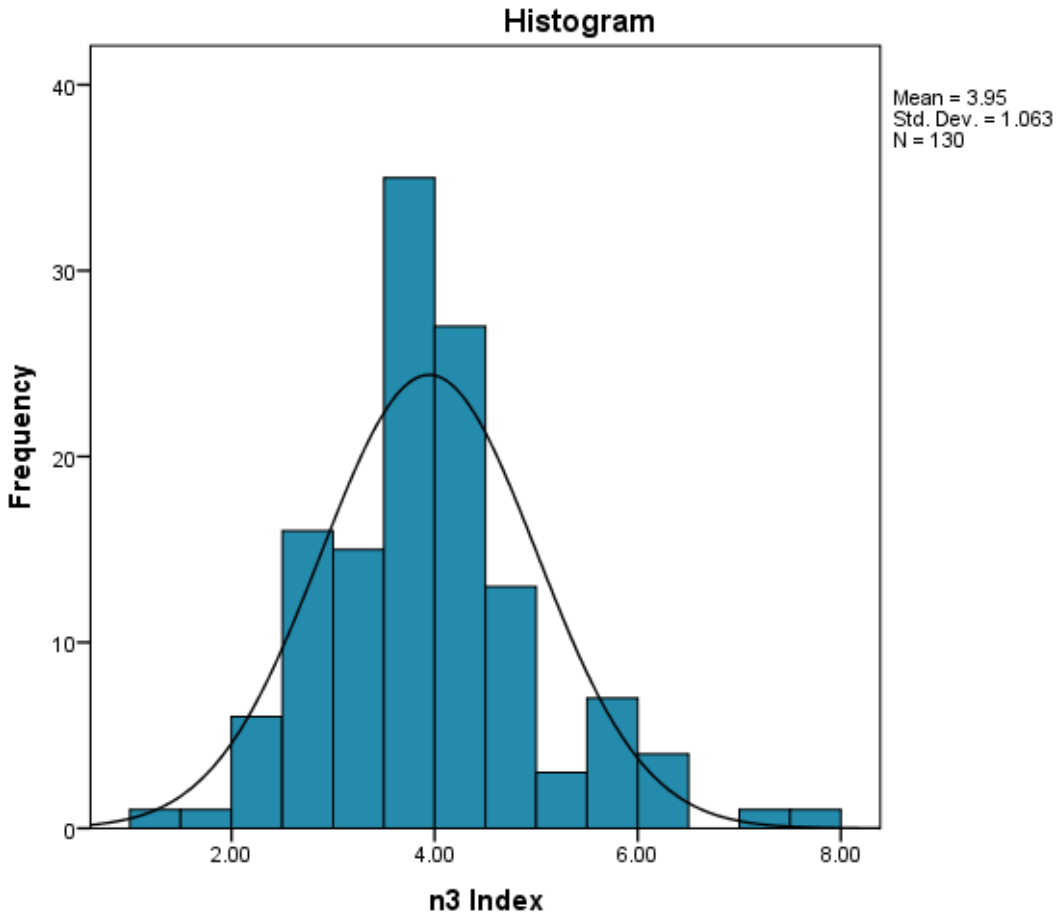

Figure 1: Distribution of the omega-3 index

Table 1: Summary characteristics, omega-3 index, omega-6 and omega-3 polyunsaturated fatty acid levels of study participants (*N*=130)

	Reference range	CRC		Mood Study	
		n	*M* (*SD*)	*n*	*M* (*SD*)
Age	n/a	14	29.00 (11.29)	118	43.90 (13.07)
Gender	n/a	14	71.4% male	118	28% male
Fasting blood glucose	4-6 mmol/L	11	6.15 (0.95)	-	N/A
Waist circumference (male)	< 94 cm	9	107.78 (22.58)	31	102.67 (19.71)
Waist circumference (female)	< 80 cm	3	91.33 (13.43)	81	93.72 (19.82)
BMI (weight/height^2)	18.5-25 [> 30 = obese]	10	30.97 (6.53)	112	30.77 (8.13)
Diastolic blood pressure	< 80 mmHg	9	74.83 (9.09)	111	80.06 (10.25)
Systolic blood pressure	< 120 mmHg	9	112.44 (11.58)	111	120.98 (15.42)
Omega-3 index (EPA + DHA)	≤ 4% ↑ risk; ≥ 8% ↓ risk for CVD mortality	14	4.04 (0.63)	116	3.92 (1.09)

CRC = Community Rehabilitation Centre (participants with schizophrenia); Mood Study = community dwelling participants with diagnosed depression and/or severe/extremely severe depression scores on the 21-item Depression Anxiety Stress Scale (DASS-21).

Pearson correlations between the omega-3 index, mental health and health-related quality of life are shown in Table 2. There were no significant associations between the omega-3 index and mental health, quality of life or cardiometabolic health outcomes. Therefore it was not possible to run regression analyses as planned.

Table 2: Pearson correlations between erythrocyte fatty acids, mental health and health-related quality of life, *N*=116-130†

	Omega-3 index
Depression (DASS)	-0.058
Anxiety (DASS)	-0.048
Stress (DASS)	-0.144
Positive affect (PANAS)	0.084
Negative affect (PANAS)	-0.001
AQoL Independent living	0.119
AQoL Happiness	0.024
AQoL Mental health	0.026
AQoL Coping	-0.004
AQoL Relationships	-0.011
AQoL Self worth	0.140
AQoL Pain	-0.017
AQoL Senses	-0.080
AQoL Super dimension psycho-social	-0.013
AQoL Super dimension physical health	0.020
Systolic blood pressure (mmHg)	-0.068
Diastolic blood pressure (mmHg)	-0.045
Body mass index (BMI; h/m^2)	-0.117
Waist circumference	-0.021
Apolipoprotein B/A1 ratio	0.049

*$p < 0.05$; **$p < 0.01$. †N varies due to missing data on individual subscales and/or some scales only completed by Mood Study cohort. DASS = Depression, Anxiety, Stress Scale (21-item); PANAS = Positive And Negative Affect Scale; AQoL = Assessment of Quality of Life 8-d scale

DISCUSSION

In this study we analysed PUFA data from people with SMI, i.e. schizophrenia and severe depressive symptoms, and determined their overall omega-3 index to be less than 4% which is in the range that has been identified as high risk for mortality from CVD [16]. We know that n-3 PUFA intake in Western societies is low generally, and this could be a contributor to the high global mortality from CVD [42]. The average omega-3 index in the Australian population is 5% [36, 43]. In our population of people with mental illness, the omega-3 index is even lower, potentially placing them at greater risk for mortality from CVD. Consistent with this, our sample of people with mental illness had, on average, risk factors for metabolic syndrome and CVD including elevated blood glucose, BMI in the obese range and excessive abdominal adiposity. However these did not correlate with the omega-3 index. A review by von Schacky reported an omega-3 index of between 2.90-7.15% in a range of populations in western countries (with high incidence of CHD) and 3.47-12.83% in Asian countries (with low incidence of CHD). In all studies low omega-3 index was associated with a worse health condition. In addition to those cited in the review, a Korean study reported an omega-3 index of 8.83% in patients with acute STEMI compared to 11.13% in healthy controls, and the omega-3 index was inversely associated with the odds for being a STEMI patient [44]. A meta-analysis by Lin et al reported lower EPA and DHA in depressed patients than controls (actual levels not reported). McNamara et al. found a lower omega-3 index in American patients with major depressive disorder (3.8% ± 0.2) and bipolar disorder (3.3% ± 0.2) compared with healthy controls (4.8% ± 0.3) [45].

As outlined earlier, a number of mechanisms have been identified for the roles of n-3 LCPUFA in the brain [18, 21] that include potentially vascular mechanisms which may

underlie both cardiovascular and mental health [19]. Further supportive of this, Canadian researchers investigated n-3 PUFA levels in people who had suffered an acute myocardial infarction and found that those who suffered major depression had notably lower n-3 PUFA levels and omega-3 index (4.46%) than those without depression (5.05%) [46]. Another very interesting study showed in a rat model that a high fructose drink increased triglycerides and insulin resistance in the brain, and that this effect was attenuated with an n-3 rich diet. Furthermore, increased insulin resistance and triglyceride levels were associated with poorer performance on a cognitive task. The authors suggested that this may provide evidence of metabolic syndrome in the brain, which is exacerbated by n-3 PUFA deficiency [47]. Therefore there may be utility in translation of the omega-3 index from cardiovascular to mental health.

Similarly to McNamara et al. [45], and as with our cardiometabolic health outcomes, there were no associations between the omega-3 index and mental health or quality of life. This may be either because there is no association with the measures used in the sample or because these n-3 PUFA levels were too low across the population. This would need to be investigated further in a sample with greater variability in omega-3 levels, across the low and high risk range for mortality from CHD.

The low levels of n-3 LCPUFAs EPA and DHA in this sample of people with mental illness and CVD risk factors is of concern. Given the role of these PUFAs in cardiovascular and mental health, this is an issue that requires further consideration in terms of developing a strong evidence base for translation into policy and practice. The direct roles of n-3 LCPUFAs, particularly DHA, in brain function and growing evidence of their ability to reduce symptoms of mental illness suggest that an omega-3 index or its equivalence might

similarly provide a useful target for estimating risk of mental illness and targets for treatment. As well as being a good indicator of n-3 PUFA levels in cardiac tissue, erythrocyte levels correspond to those found in brain tissue [48]. More studies are needed to establish baseline erythrocyte n-3 and n-6 PUFA levels that are associated with highest risk of mental illness, and correlate increased levels following n-3 PUFA supplementation with improved mental health outcomes to determine levels that are associated with greatest protection. It would be useful for intervention studies to be conducted over at least 6 months to enable maximum saturation of cell membranes [49], recruit people with low omega-3 index with the aim of reaching the target range (> 8%) [42] and to identify critical periods that provide maximum opportunity for prevention, e.g. in teenage years for young people at high risk for psychosis, when n-3 PUFA supplementation appears to provide optimal protection against transition to psychosis [22].

In conclusion, the omega-3 index was very low in this population of people with SMI. This is of concern given the associations between such a low omega-3 index and increased risk of mortality from CVD.

Acknowledgements

We acknowledge and thank the team at the TPC for their support of study 1 and assistance in obtaining blood samples from their consumers. We gratefully thank Louise Massie and the Sansom Health Clinic for support with clinic visits and administration associated with study 2, Lauren Roach for assistance with fatty analysis and all participants for taking part. NP (formerly Sinn), DZ and AW are supported by NHMRC Program Grant funding (# 320860 and 631947). Epax, Pathway International, Edgell, John West and Cobram Estate provided fish oil supplements, food and extra virgin olive oil for Study 2 from which these baseline data are derived.

NP, KO, NPr, JS and AC conceived and designed the study; DM, AW, MB, JC and AV collected the data; NP and BM analysed the data; BM contributed reagents/materials; NP wrote the paper and all authors provided input and approved the final paper. We declare no conflicts of interest.

References

[1] World Health Organisation, The World Health Report: Mental health - new understandings, new hope, in, World Health Organisation, Geneva, 2001.

[2] R.C. Kessler, S. Aguilar-Gaxiola, J. Alonso, S. Chatterji, S. Lee, J. Ormel, T.B. Üstün, P.S. Wang, The global burden of mental disorders: An update from the WHO World Mental Health (WMH) Surveys, Epidemiol. Psichiatr. Soc., 18 (2009) 23-33.

[3] D.P. Osborn, The poor physical health of people with mental illness, West. J. Med., 175 (2001) 329-332.

[4] M. De Hert, C.U. Correll, J. Bobes, M. Cetkovich-Bakmas, D. Cohen, I. Asai, J. Detraux, S. Gautam, H.-J. Möller, D.M. Ndetei, J.W. Newcomer, R. Uwakwe, S. Leucht, Physical illness in patients with severe mental disorders. I. Prevalance, impact of medications and disparities in health care, World Psychiatry, 10 (2011) 52-77.

[5] M.J. Knol, J.W. Twisk, A.T. Beekman, R.J. Heine, F.J. Snoek, F. Pouwer, Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis, Diabetologia, 49 (2006) 837-845.

[6] A. Pan, N. Keum, O.I. Okereke, Q. Sun, M. Kivimaki, Bidirectional association between depression and metabolic syndrome: A systematic review and meta-analysis of epidemiological studies, Diabetes Care, 35 (2012) 1171-1180.

[7] N. Parletta, Y. Aljeesh, B.T. Baune, Health behaviours, knowledge, life satisfaction and wellbeing in people with mental illness across four countries and comparisons with normative sample, (under review).

[8] D.P.J. Osborn, I. Nazareth, M.B. King, Physical activity, dietary habits and Coronary Heart Disease risk factor knowledge amongst people with severe mental illness, Soc. Psychiatry Psychiatr. Epidemiol., 42 (2007) 787-793.

[9] M. Peet, Diet, diabetes and schizophrenia: review and hypothesis, Br J. Psychiatry., 184 (2004) s102-s105.

[10] J.S. Lai, S. Hiles, A. Bisquera, A.J. Hure, M. McEvoy, J. Attia, A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults, Am. J. Clin. Nutr., 99 (2014) 181-197.

[11] M. Peet, International variations in the outcome of schizophrenia and the prevalence of depression in relation to national dietary practices: an ecological analysis, Br J. Psychiatry., 184 (2004) 404-408.

[12] A.H. Lichtenstein, L.J. Appel, M. Brands, M. Carnethon, S. Daniels, H.A. Franch, B. Franklin, P. Kris-Etherton, W.S. Harris, B. Howard, N. Karanja, M. Lefevre, L. Rudel, F. Sacks, L. Van Horn, M. Winston, J. Wylie-Rosett, Diet and lifestyle recommendations revision 2006: A scientific statement from the American Heart Association Nutrition Committee, Circulation, 114 (2006) 82-96.

[13] M.J. James, T.R. Sullivan, R.G. Metcalf, L.G. Cleland, Pitfalls in the use of randomised controlled trials for fish oil studies with cardiac patients, Br. J. Nutr., 112 (2014) 812-820.

[14] H.B. Rice, A. Bernasconi, K.C. Maki, W.S. Harris, C. Von Schacky, P.C. Calder, Conducting omega-3 trials with cardiovascular outcomes: Proceedings of a workshop held at ISSFAL 2014, Prostaglandins Leukot. Essent. Fatty Acids. http://dx.doi.org/10.1016/j.plefa.2016.01.003 (2016).

[15] P. Kris-Etherton, W.S. Harris, L.J. Appel, for the Nutrition Committee, AHA Scientific Statement: Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease, Circulation, 106 (2002) 2747-2757.

[16] W.S. Harris, C. von Schacky, The Omega-3 Index: a new risk factor for death from coronary heart disease?, Prev. Med., 39 (2004) 212-220.

[17] A.J. Sinclair, M.A. Crawford, The accumulation of arachidonate and docosahexaenoate in the developing rat brain, J. Neurochem., 19 (1972) 1753-1758.

[18] N. Parletta, C.M. Milte, B. Meyer, Nutritional modulation of cognitive function and mental health, J. Nutr. Biochem., 24 (2013) 725-743.

[19] N. Sinn, P.R.C. Howe, Mental health benefits of omega-3 fatty acids may be mediated by improvements in cerebral vascular function, Biosci. Hypotheses., 1 (2008) 103-108.

[20] M.P. Freeman, J.R. Hibbeln, K.L. Wisner, J.M. Davis, D. Mischoulon, M. Peet, P.E. Keck, L.B. Marangell, A.J. Richardson, J. Lake, A.L. Stoll, Omega-3 fatty acids: Evidence base for treatment and future research in psychiatry, J. Clin. Psychiatry, 67 (2006) 1954-1967.

[21] N. Sinn, C. Milte, P.R.C. Howe, Oiling the brain: A review of randomised controlled trials of omega-3 fatty acids in psychopathology across the lifespan, Nutrients, 2 (2010) 128-170.

[22] P.G. Amminger, M.R. Schäfer, K. Papageorgiou, C.M. Klier, S.M. Cotton, S.M. Harrigan, A. Mackinnon, P. McGorry, G.E. Berger, Long-chain ω-3 fatty acids for indicated prevention of psychotic disorders, Arch. Gen. Psychiatry, 67 (2010) 146-154.

[23] C. Milte, N. Sinn, P.R.C. Howe, Polyunsaturated fatty acid status in ADHD, depression and dementia: towards an omega-3 index for mental health?, Nutr. Rev. 67 (2009) 573-590.

[24] M.B. Howren, D.M. Lamkin, J. Suls, Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis, Psychosom. Med., 71 (2009) 171-186.

[25] Y. Dowlati, N. Herrmann, W. Swardfager, H. Liu, L. Sham, E.K. Reim, K.L. Lanctot, A meta-analysis of cytokines in major depression, Biol. Psychiatry, 67 (2010) 446-457.

[26] D. Gimeno, M. Kivimaki, E.J. Brunner, M. Elovainio, R. De Vogli, A. Steptoe, M. Kumari, G.D.O. Lowe, A. Rumley, M.G. Marmot, J.E. Ferrie, Associations of C-reactive

protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study, Psychol. Med., 39 (2009) 413-423.

[27] J.A. Pasco, G.C. Nicholson, L.J. Williams, F.N. Jacka, M.J. Henry, M.A. Kotowicz, H.G. Schneider, B.E. Leonard, M. Berk, Association of high-sensitivity C-reactive protein with *de novo* major depression, Br J. Psychiatry, 197 (2010) 372-377.

[28] B.S. Fernandes, J. Steiner, H.-G. Bernstein, S. Dodd, J.A. Pasco, O.M. Dean, P. Nardin, C.-A. Goncalves, M. Berk, C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications, Mol Psychiatry, doi:10.1038/mp.2015.87 (2015).

[29] B.J. Meyer, N. Kolanu, Australian children are not consuming enough long-chain omega-3 polyunsaturated fatty acids for optimal health, Nutrition, 27 (2011) 1136-1140.

[30] B.J. Meyer, N.J. Mann, J.L. Lewis, G.C. Milligan, A.J. Sinclair, P.R.C. Howe, Dietary intakes and food sources of omega-6 and omega-3 polyunsaturated fatty acids, Lipids, 38 (2003) 391-398.

[31] A.P. Simopoulos, Omega-3 fatty acids in wild plants, nuts and seeds, Asia Pac. J. Clin. Nutr., 11 (2002) S163-S173.

[32] S. Bogomolova, D. Zarnowiecki, A. Wilson, A. Fielder, N. Procter, C. Itsiopoulos, K. O'Dea, J. Strachan, M. Ballestrin, A. Champion, N. Parletta, Dietary intervention for people with mental illness in South Australia, (under review).

[33] D. Zarnowiecki, J. Cho, A.M. Wilson, S. Bogomolova, A. Villani, C. Itsiopoulos, T. Niyonsenga, K. O'Dea, S. Blunden, B.J. Meyer, L. Segal, N. Parletta, A 6-month randomised controlled trial investigating effects of Mediterranean-style diet and fish oil supplementation on dietary behaviour change, mental and cardiometabolic health and health-related quality of life in adults with depression (HELFIMED): Study protocol, (under review).

[34] J.D. Henry, J.R. Crawford, The short-form version of the Depression Anxiety Stress Scales (DASS-21): Construct validity and normative data in a large non-clinical sample, Br. J. Clin. Psychol., 44 (2005) 227-239.

[35] J. Richardson, G. Elsworth, A. Iezzi, M.A. Khan, C. Mihalopoulos, I. Schweitzer, H. Herrman, Increasing the sensitivity of the AQoL inventory for the evaluation of interventions affecting mental health, in, Monash University, 2011.

[36] M. Swierk, P.G. Williams, J. Wilcox, K.G. Russell, B.J. Meyer, Validation of an Australian electronic food frequency questionnaire to measure polyunsaturated fatty acid intake, Nutrition, 27 (2011) 641-646.

[37] G. Lepage, C.C. Roy, Direct transesterification of all classes of lipids in a one-step reaction, J. Lipid Res., 27 (1986) 114-120.

[38] J. Richardson, A. Iezzi, M.A. Khan, A. Maxwell, Validity and reliability of the Assessment of Quality of Life (AQoL)-8D multi-attribute utility instrument, The Patient, 7 (2014) 85-96.

[39] J.R. Crawford, C. Cayley, P.F. Lovibond, P.H. Wilson, C. Hartley, Percentile norms and accompanying interval estimates from an Australian general adult population sample for self-report mood scales (BAI, BDI, CRSD, CES-D, DASS, DASS-21, STAI-X, STAI-Y, SRDS, and SRAS), Aust. Psychol., 46 (2011) 3-14.

[40] S.H. Lovibond, P.F. Lovibond, Manual for the Depression Anxiety Stress Scales, 2nd edition, Psychology Foundation, Sydney, 1995.

[41] J.R. Crawford, J.D. Henry, The Positive and Negative Affect Schedule (PANAS): Construct validity, measurement properties and normative data in a large non-clinical sample, Br. J. Clin. Psychol., 43 (2004) 245-265.

[42] C. von Schacky, Omega-3 index and cardiovascular health, Nutrients, 6 (2014) 799-814.

[43] B.L. Sullivan, P.G. Williams, B.J. Meyer, Biomarker validation of a long-chain omega-3 polyunsaturated fatty acid food frequency questionnaire, Lipids, 41 (2006) 845-850.

[44] Y.J. Kim, D.W. Jeong, J.G. Lee, H.C. Lee, S.Y. Lee, Y.J. Kim, Y.H. Yi, Y.S. Park, Y.H. Cho, M.J. Bae, E.J. Choi, Omega-3 index and smoking in patients with acute ST-elevation myocardial infarction taking statins: a case-control study in Korea, Lipids Health Dis., 11 (2012) http://www.lipidworld.com/content/11/11/43.

[45] R.K. McNamara, R. Jandacek, T. Rider, P. Tso, Y. Dwivedi, G.N. Pandey, Selective deficits in erythrocyte docosahexaenoic acid composition in adult patients with bipolar disorder and major depressive disorder, J. Affect. Disord., 126 (2010) 303-311.

[46] N. Frasure-Smith, F. Lespérance, P. Julien, Major depression is associated with lower omega-3 fatty acid levels in patients with recent acute coronary syndromes, Biol. Psychiatry, 55 (2004) 891-896.

[47] R. Agrawal, F. Gomez-Pinilla, 'Metabolic syndrome' in the brain: deficiency in omega-3 fatty acid exacerbates dysfunctions in insulin receptor signalling and cognition, J. Physiol., 590 (2012) 2485-2499.

[48] C.N. Kuratko, N. Salem, Biomarkers of DHA status, Prostaglandins Leukot. Essent. Fatty Acids, 81 (2009) 111-118.

[49] M.B. Katan, J.P. Deslypere, A.P. van Birgelen, M. Penders, M. Zegwaard, Kinetics of the incorporation of dietary fatty acids into serum cholesteryl esters, erythrocyte membranes, and adipose tissue: an 18-month controlled study, J. Lipid Res., 38 (1997) 2012-2022.