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## Dietary intake of fish and PUFA, and clinical depressive and anxiety disorders in women

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### Abstract

Fish and PUFA consumption are thought to play a role in mental health; however, many studies do not take into account multiple sources of PUFA. The present study analysed data from a sample of 935 randomly selected, population-based women aged 20–93 years. A validated and comprehensive dietary questionnaire ascertained the consumption of *n*-3 and *n*-6 PUFA. Another assessed fish and energy intake and provided data for a dietary quality score. The General Health Questionnaire-12 (GHQ-12) measured psychological symptoms and a clinical interview (Structured Clinical Interview for DSM-IV-TR Research Version, Non-patient edition) assessed depressive and anxiety disorders. Median dietary intakes of long-chain *n*-3 fatty acids (310 mg/d) were below suggested dietary target levels. The only PUFA related to categorical depressive and anxiety disorders was DHA. There was a non-linear relationship between DHA intake and depression; those in the second tertile of DHA intake were nearly 70% less likely to report a current depressive disorder compared to those in the first tertile. The relationship of DHA to anxiety disorders was linear; for those in the highest tertile of DHA intake, the odds for anxiety disorders were reduced by nearly 50% after adjustments, including adjustment for diet quality scores, compared to the lowest tertile. Those who ate fish less than once per week had higher GHQ-12 scores, and this relationship was particularly obvious in smokers. These are the first observational data to indicate a role for DHA in anxiety disorders, but suggest that the relationship between DHA and depressive disorders may be non-linear.

**Key words:** *n*-3: *n*-6: PUFA: Depression: Anxiety: Diet: Nutrition

Linoleic acid (LA; 18:2*n*-6) and  $\alpha$ -linolenic acid (ALA; 18:3*n*-3) are considered essential PUFA, in that they cannot be created by the body and must be consumed in the diet<sup>(1)</sup>. LA is predominantly derived from vegetable oils, such as sesame, cottonseed and sunflower oils, whereas ALA is largely derived from plant foods such as walnuts, vegetables, legumes, grains and rapeseed oil<sup>(2)</sup>. These PUFA are synthesised endogenously to create the main long-chain (LC) *n*-6 PUFA, arachidonic acid (AA; 20:4*n*-6), the LC *n*-3 PUFA EPA (20:5*n*-3), docosapentaenoic acid (DPA; 22:5*n*-3) and DHA (22:6*n*-3), although the conversion of LA to AA is

far more efficient than that of ALA to EPA and DHA<sup>(3)</sup>. The LC-PUFA can also be obtained directly from the diet; fish and seafood are the major dietary sources of EPA and DHA. Recently, it has been established that beef and lamb, which are usually grass-fed in Australia, are also an important source of *n*-3 PUFA in the Australian diet, contributing nearly half of the average intake of LC *n*-3 PUFA in the form of DPA<sup>(4)</sup>.

Several lines of evidence indicate that a relationship exists between *n*-3 and *n*-6 PUFA and mental health. For example, numerous studies in clinical populations have demonstrated

**Abbreviations:** AA, arachidonic acid; ALA,  $\alpha$ -linolenic acid; DPA, docosapentaenoic acid; DQS, diet quality score; GHQ-12, General Health Questionnaire-12; IQR, interquartile range; LA, linoleic acid; LC, long-chain; NHMRC, National Health and Medical Research Council; SCID-I/NP, Structured Clinical Interview for DSM-IV-TR Research Version, Non-patient edition; SES, socio-economic status.

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reduced levels of *n*-3 PUFA and increased ratios of *n*-6:*n*-3 in patients with major depression compared to healthy controls<sup>(5–9)</sup>. However, trials of LC *n*-3 PUFA supplementation in depression have yielded equivocal results. A very recent meta-analysis determined that there was a very small beneficial effect of treatment with *n*-3 compared to placebo, but that the benefit of supplementation was only observable in those with clinical depression, in particular those with more severe depression<sup>(10)</sup>. It was concluded that increased *n*-3 PUFA consumption, via fish intake or supplementation, would be of little benefit to the general population. Nonetheless, in several population studies, low levels of fish and/or *n*-3 PUFA consumption are associated with increased depression<sup>(11–16)</sup>, although a linear relationship has not always been observed<sup>(17–20)</sup>.

Previous studies in this field have concentrated on the dietary intakes of fish and/or *n*-3 PUFA EPA and DHA, and have not additionally measured DPA, *n*-6 PUFA or *n*-3 PUFA from vegetable sources such as nuts and seeds. Moreover, most studies have not accounted for overall energy intake, which may confound or obscure the relationship between PUFA and mental health<sup>(21)</sup>. Furthermore, most, but not all<sup>(16)</sup>, previous studies failed to examine measures of overall diet quality as a confounding factor in the relationship between PUFA/fish consumption and mental health<sup>(22)</sup>. Finally, there are no existing observational studies of the relationship between dietary intakes of PUFA and anxiety disorders which, together with depression, comprise the common mental disorders. In the present study, we aimed to examine the associations between the consumption of both vegetable and animal sources of *n*-3 and *n*-6 PUFA, fish consumption and clinically determined depressive and anxiety disorders, as well as psychological symptoms, in a randomly selected, population-based sample of adult women. We further aimed to test overall diet quality as an explanatory variable in any relationship of fish and/or PUFA intake to mental health outcomes.

## Methods

### Participants

The Geelong Osteoporosis Study is a large epidemiological study involving women selected from compulsory Australian Commonwealth electoral rolls for the Barwon Statistical Division. An age-stratified, randomly selected, population-based sample of women (aged 20–94 years) was recruited between 1994 and 1997, with a minimum of 100 in each 5-year age stratum between the ages of 20 and 69 years, and a minimum of 200 in the 70–79-year age group and in the over 80-year age group, with an original participation rate of 77.1%. Reasons for non-participation included death, migration from the region, inability to give informed consent, pregnancy or inability to be contacted. In order to afford continuing investigation of the full adult age range, an additional sample of 200 women aged between the ages of 20 and 29 years was recruited in 2004–2008, with a response of 70.9%. These women have continued to return for biennial follow-up assessments<sup>(23)</sup>. Of the 1127 women who

participated in the Geelong Osteoporosis Study 10-year follow-up, participants for whom psychiatric or PUFA data were not available (*n* 192) were excluded from the study, resulting in a sample of 935 women aged 20–93 years available for analysis. The present study was conducted according to the guidelines laid down in the Declaration of Helsinki, and the Barwon Health Human Research Ethics Committee approved all procedures involving human subjects. Written informed consent was obtained from all participants.

### Dietary assessment

Habitual diet quality, fish consumption and energy intake were assessed with the Cancer Council dietary questionnaire<sup>(24)</sup>. This is a comprehensive optically scannable FFQ, validated for assessing habitual dietary intake in the Australian population<sup>(25)</sup>. This FFQ asked participants to report their usual consumption of seventy-four foods and six alcoholic beverages over the preceding 12 months using a ten-point frequency scale. Using the estimated portions sizes, intakes of each food were converted to daily equivalents for statistical analyses. Nutrient intakes, including energy, were computed from the FFQ data using an in-house program, developed by the Cancer Council Victoria using NUTTAB95<sup>(26)</sup> nutrient composition data.

### PUFA FFQ

The semi-quantitative PUFA FFQ is a validated electronic questionnaire designed to assess main food sources of *n*-3 and *n*-6 PUFA<sup>(27)</sup>. The PUFA FFQ consisted of thirty-eight questions regarding the usual dietary habits related to PUFA intake over the previous 3 months. The questions were specific to food items that are animal sources of PUFA, such as fish, meat and eggs, and plant sources of PUFA, including vegetable oils, nuts and seeds. Categories of food included breads/cereals, fish/seafood, meat, eggs, nuts and desserts. Fish oil capsule consumption was also ascertained by the questionnaire, as well as products with enriched LC *n*-3 such as bread, eggs and milk. Questions regarding the frequency of consumption included several choices, ranging from never to intakes per d, week or month.

### Diet quality score

An *a priori* diet quality score (DQS) was derived from the Cancer Council FFQ, based on the Australian national guidelines for healthy eating<sup>(28)</sup> and on an algorithm previously validated in Australian women<sup>(29)</sup>. This scoring method assigned points for the consumption of desirable foods at the recommended levels; for example, a point was assigned for the consumption of at least two fruit serves per d; at least five serves of vegetables per d; red meat consumption more than once, but less than five times per week; using low-fat dairy products; using high-fibre, whole-meal, rye or multigrain breads, etc. In addition, a maximum of two points were assigned for alcohol consumption at the recommended levels<sup>(30)</sup>.

### Psychiatric assessments

The Structured Clinical Interview for DSM-IV-TR Research Version, Non-patient edition (SCID-I/NP)<sup>(31)</sup> was the primary diagnostic instrument for the common mental disorders. This is the 'gold-standard' assessment tool comprising a validated, semi-structured clinical interview for the major Axis I psychiatric disorders in DSM-IV-TR. Diagnoses of current major depressive disorder, dysthymia and anxiety disorders (panic disorder, agoraphobia, social phobia, specific phobia, obsessive-compulsive disorder, generalised anxiety disorder, anxiety disorders due to a general medical condition, substance-induced anxiety disorders and anxiety disorders not otherwise specified) were the outcomes of interest of the present study. Researchers trained in psychology and administration of the SCID-I/NP conducted these interviews. Psychological symptoms were measured with the self-reported General Health Questionnaire-12 (GHQ-12)<sup>(32)</sup>.

### Covariates

Socio-economic status (SES) was determined using Socio-economic Index For Areas index scores based on the 2006 Australian Bureau of Statistics census data. It was decided *a priori* to use the Index of Relative Socio-economic Advantage and Disadvantage, which accounts for high and low income and the type of occupation from unskilled employment to professional positions. A low score on this index identifies the most disadvantaged (quintile 1) and a high score identifies the most advantaged (quintile 5). Physical activity was assessed by self-report questionnaire and ranged from (1) chair or bed-ridden or limited activity throughout the home through to (4) very active. Alcohol consumption in g/d was ascertained from the dietary questionnaire and was subsequently categorised according to 2001 recommendations for women<sup>(30)</sup> as the following: zero consumption (1), one to fourteen standard drinks per week (2) and fifteen or more standard drinks per week (3). Current cigarette smoking (yes/no) was self-reported. Energy intake (kJ/d) was determined from the FFQ. Height was measured to the nearest 0.1 cm and body weight was measured to the nearest 0.1 kg. BMI was calculated from these measurements as weight/height<sup>2</sup> (kg/m<sup>2</sup>).

### Statistical analysis

Differences in characteristics and dietary intakes between those with and without categorical diagnoses on the SCID-I/NP were tested using *t* tests, Mann-Whitney tests or the  $\chi^2$  test. DQS were normally distributed; however, all PUFA variables and GHQ-12 scores were positively skewed. PUFA intakes could not be transformed and were thus categorised into tertiles, which allowed for an examination of non-linear relationships. Fish in g/d and GHQ-12 scores were normalised using natural log transformations, standardised using *z*-scores and subsequently expressed as standard deviation units. Frequency of fish consumption was also examined, with the dichotomous variable classified as fish consumption once a

week or more, compared to fish consumption less than once per week.

Multivariable linear regression analyses were used to assess the relationship of the exposure variables of interest and GHQ-12 scores. Logistic regression models were developed to estimate OR with 95% CI using current major depressive disorder/dysthymia and anxiety disorders as the outcomes of interest. PUFA and fish consumption, in both g/d and as a dichotomous frequency variable, were the exposure variables of interest. For each analysis, the following covariates were entered sequentially in order to test their contribution to the mental health outcomes: age, SES, health behaviours (physical activity, alcohol consumption and smoking), energy intake and, finally, DQS. BMI and antidepressant use were also tested in the models as explanatory variables. Smoking, antidepressant use and BMI (<25 or  $\geq$ 25) kg/m<sup>2</sup> were tested as effect modifiers.

There were no missing data on dietary variables. There were missing data for GHQ-12 scores (*n* 21) and list-wise exclusions were used when GHQ-12 was the outcome variable, resulting in a sample of 914 women for these analyses. There were twenty-five participants with missing data on BMI. There were no missing data on any other variables.

## Results

### Dietary intakes

Median dietary intakes of AA were 140 mg/d. Those of LA were 6.7 g/d (interquartile range (IQR) 5.0–9.8) and of ALA were 0.95 g/d (IQR 0.55–1.25), which were comparable to the adequate intake of 8 and 0.8 g/d, respectively, for Australian women<sup>(1)</sup>. Median intakes of the *n*-3 PUFA EPA, DHA and DPA were 310 mg/d (IQR 210–480 mg/d), which exceeds the adequate intake of 90 mg/d for Australian women, but falls short of the suggested dietary target of 430 mg/d. The National Health and Medical Research Council (NHMRC) definition of adequate intake is based on mean/median population intakes<sup>(33)</sup> and not on physiological need, whereas the suggested dietary target is defined as 'the daily average intake from food and beverages for certain nutrients that may help in prevention of chronic disease'<sup>(1)</sup>. DQS were normally distributed (mean 31 (SD 8.5)), while GHQ-12 scores were slightly positively skewed (median 22, IQR 20–25). Slightly more than half of the participants (51%) consumed fish once or more per week.

Characteristics of those with and without categorical diagnoses on the SCID-I/NP are given in Table 1. There were fifty-one (5.5%) individuals with current depressive disorders and sixty-six (7.1%) with current anxiety disorders. There were thirty-four women (3.6%) with depressive disorders only; forty-nine women (5.2%) with only anxiety disorders; and seventeen women (1.8%) with both. Those with current anxiety disorders were younger than those without, while those with a current depressive disorder were more likely to smoke than those without. Otherwise, there were no differences between groups on Socio-economic Index For Areas scores, physical activity, alcohol or energy intake and BMI.

**Table 1.** Characteristics of study sample: comparisons between those with and without depressive/anxiety disorders (Mean values and standard deviations; number of participants and percentages)

	MDD/dysthymia (n 51)		No depressive disorder (n 884)		P	Anxiety disorder (n 66)		No anxiety disorder (n 869)		P
	n	%	n	%		n	%	n	%	
Age (years)					0.73					0.05
Mean		50.7		51.9			47.4		52.2	
SD		12.9		19.1			16.0		18.9	
BMI (kg/m <sup>2</sup> )					0.20					0.94
Mean		28.0		27.3			27.2		27.4	0.94
SD		5.2		5.7			5.6		5.7	
Smoking (current)	11	21.6	104	11.8	0.04	11	16.7	104	12.0	0.26
Physical activity (active or very active)	35	68.6	695	78.6	0.46	46	69.7	684	78.7	0.21
Energy (kJ/d)					0.60					0.28
Mean		6935.8		6634.0			6804.1		6638.8	
SD		2928.4		2255.9			2223.0		2303.1	
SES (1 = low)					0.79					0.43
1	8	15.7	136	15.4		8	12.1	136	15.7	
2	8	15.7	186	21.0		11	16.7	183	21.1	
3	14	27.5	202	22.9		15	22.7	201	23.1	
4	12	23.5	175	19.8		19	28.8	168	19.3	
5	9	17.6	185	20.9		13	19.7	181	20.8	
Alcohol (drinks/week)					0.34					0.85
0	13	25.5	169	19.1		14	21.2	168	19.3	
1–14	29	56.9	591	66.9		44	66.7	576	66.3	
15+	9	17.6	124	14.0		8	12.1	125	14.4	
Fish oil supplement use	12	23.5	133	15.0	0.10	14	21.2	131	15.1	0.18

MDD, major depressive disorder; SES, socio-economic status.

There were no significant differences between those with and without current depressive and/or anxiety disorders in any of the PUFA or fish consumption variables (Table 2).

### Categorical diagnoses

In multivariable analyses examining PUFA and depressive and anxiety disorders, the only identified confounders were energy intake and DQS, and all logistic regression analyses were adjusted for these variables. There were no relationships observed between the frequency of fish consumption or fish in g/d and either depressive or anxiety disorders (data not

shown). Moreover, there were no relationships detected among the intakes of LA, AA, ALA, EPA or DPA or ratios of *n-6:n-3* and depressive and/or anxiety disorders. The only apparent relationships observed were between intakes of DHA and anxiety and depressive disorders (Table 3.) For those in the highest tertile of DHA intake, the odds for anxiety disorders were reduced by nearly half compared to the lowest tertile, and the relationship between the variables was linear ( $P$  for trend=0.045). In contrast, the relationship between DHA intake and depressive disorders was non-linear. For those in the second tertile of DHA intake, the odds for current depression were reduced by nearly 70% compared to the

**Table 2.** PUFA and fish intakes: comparisons between those with and without depressive/anxiety disorders (Medians and interquartile ranges (IQR))

	MDD/dysthymia (n 51)		No depressive disorder (n 884)		P	Anxiety disorders (n 66)		No anxiety disorder (n 869)		P
	Median	IQR	Median	IQR		Median	IQR	Median	IQR	
PUFA (g/d)										
LA	7.3	4.7–10.7	6.7	5.0–9.8	0.99	6.2	4.4–10.8	6.8	5.0–9.8	0.62
AA	0.15	0.10–0.24	0.14	0.10–0.20	0.63	0.14	0.08–0.17	0.14	0.10–0.20	0.15
ALA	0.85	0.56–1.33	0.77	0.55–1.25	0.72	0.72	0.52–1.06	0.78	0.55–1.27	0.29
EPA	0.11	0.05–0.18	0.09	0.06–0.14	0.65	0.08	0.05–0.12	0.09	0.06–0.14	0.07
DPA	0.08	0.05–0.13	0.08	0.05–0.11	0.74	0.07	0.05–0.11	0.08	0.06–0.12	0.18
DHA	0.14	0.07–0.26	0.13	0.08–0.22	0.75	0.13	0.06–0.18	0.13	0.08–0.26	0.11
LC- <i>n-3</i> total	0.36	0.17–0.54	0.31	0.21–0.48	0.74	0.29	0.18–0.41	0.31	0.21–0.49	0.15
<i>n-3</i> Total	1.36	0.86–1.67	1.18	0.86–1.70	0.34	1.11	0.87–1.52	1.20	0.86–1.72	0.24
<i>n-6</i> Total	7.6	4.9–11.2	7.1	5.3–10.1	0.82	6.6	4.7–11.0	7.1	5.3–10.1	0.54
Total PUFA	8.6	6.0–12.6	8.5	6.3–12.1	0.74	8.0	5.8–12.4	8.5	6.3–12.1	0.45
<i>n-6:n-3</i>	5.3	4.1–8.3	6.0	4.4–8.0	0.64	6.6	4.3–9.2	5.9	4.4–7.9	0.24
Fish (g/d)	29	10–57	31	16–57	0.66	32	5–61	31	16–57	0.33

MDD, major depressive disorder; LA, linoleic acid; AA, arachidonic acid; ALA,  $\alpha$ -linolenic acid; DPA, docosapentaenoic acid; LC, long-chain.



**Table 3.** Results of multivariable logistic regression analyses\* (Odds ratios and 95 % confidence intervals)

	MDD/dysthymia (n 51)		Anxiety disorders (n 66)	
	OR	95 % CI	OR	95 % CI
<b>LA</b>				
Lowest (ref)	1		1	
2	0.53	0.25, 1.12	0.76	0.40, 1.46
3	0.84	0.42, 1.70	1.10	0.59, 2.07
<b>AA</b>				
Lowest (ref)	1		1	
2	0.69	0.33, 1.45	1.27	0.71, 2.28
3	0.94	0.47, 1.89	0.55	0.27, 1.23
<b>ALA</b>				
Lowest (ref)	1		1	
2	0.82	0.39, 1.69	0.83	0.45, 1.53
3	1.03	0.51, 2.08	0.71	0.37, 1.34
<b>EPA</b>				
Lowest (ref)	1		1	
2	0.80	0.37, 1.71	0.74	0.40, 1.38
3	1.31	0.64, 2.69	0.62	0.32, 1.21
<b>DPA</b>				
Lowest (ref)	1		1	
2	0.76	0.38, 1.55	0.90	0.50, 1.65
3	0.77	0.37, 1.57	0.67	0.35, 1.30
<b>DHA</b>				
Lowest (ref)	1		1	
2	0.31	0.12, 0.79	0.78	0.43, 1.42
3	1.44	0.73, 2.83	0.49	0.24, 0.98

MDD, major depressive disorder; LA, linoleic acid; ref, reference; AA, arachidonic acid; ALA,  $\alpha$ -linolenic acid; DPA, docosapentaenoic acid.

\* Depressive and anxiety disorders, adjusted for adjusted for energy intake and diet quality score.

lowest tertile, while those in the highest tertile, the likelihood was equivalent to those in the lowest. Median intakes for DHA in the first tertile were 65 (IQR 48–80) mg/d, in the second tertile were 134 (IQR 111–156) mg/d, while median intakes for the highest tertile were 272 (IQR 223–377) mg/d. Further analyses revealed that women with major depressive disorder/dysthymia or anxiety disorders tended to be more likely to take *n*-3 supplements than women with no disorder (major depressive disorder/dysthymia 23.5 *v.* 15.0%, *P*=0.10; anxiety disorders 21.2 *v.* 15.1%, *P*=0.18); however, adjustment for supplement use (yes/no) did not substantially alter the shape or strength of the observed relationships (data not shown).

**General Health Questionnaire-12 scores**

We observed a trend towards a relationship between the intake of DHA and GHQ-12 scores after adjustments for age, SES, physical activity, alcohol consumption and energy intake (compared to lowest tertile of DHA intake, tertile 2: *z*-scored  $\beta$  = -0.16, 95% CI -0.32, 0.004; tertile 3: *z*-scored  $\beta$  = -0.15, 95% CI -0.31, 0.02); however, this relationship was fully explained by adjustments for DQS. There were no relationships between the dietary intakes of any of the other PUFA and GHQ-12 scores (all *P*>0.10). Smoking was identified as an effect modifier in the relationship between fish intake and GHQ-12 scores, and these analyses were thus split by smoking status (yes/no). Before and after adjustments for age, SES, physical activity, alcohol consumption and

energy intake, the dietary intake of fish in g/d tended to be inversely related to GHQ-12 scores for both smokers and non-smokers, but the relationship was stronger in smokers. However, these relationships were also fully explained by final adjustment for DQS. In analyses examining frequency of fish intake, we report that for those women consuming fish once per week or more, there was a 0.16SD decrease in GHQ-12 scores for non-smokers and a 0.52SD decrease for smokers compared to those consuming fish less than once per week after adjustments for age, SES, physical activity, alcohol consumption and energy intake (Table 4). This relationship was attenuated by adjustment for DQS in non-smokers, but remained significant in smokers. Neither antidepressant use nor BMI was identified as a confounder or effect modifier in any analyses.

**Discussion**

In the present cross-sectional, community-based study in women, we report inverse, linear relationships between the dietary consumption of DHA and the likelihood of anxiety disorders, and a non-linear relationship between DHA intake and depressive disorders. We also observed a relationship between an increased frequency of fish consumption and reduced psychological symptoms, which was stronger in smokers. However, we failed to detect relationships between any other PUFA and these mental health parameters.

To our knowledge, the present study is the first observational study to report an association between the dietary intakes of PUFA and clinically determined anxiety disorders. However, there is some clinical and experimental evidence supporting these findings. A case-control investigation of twenty-seven untreated, non-depressed patients with social anxiety disorder reported significantly reduced levels of most *n*-3 PUFA in erythrocytes compared to healthy controls<sup>(34)</sup>, while in an experimental study, administration of

**Table 4.** Fish intake and General Health Questionnaire-12 (GHQ-12) scores split by smokers/non-smokers ( $\beta$ -Coefficients and 95 % confidence intervals)

	GHQ-12 scores (z-scored)		
	$\beta$ -Coefficient	95 % CI	<i>P</i>
<b>Fish (g/d)</b>			
Smokers (n 114)			
*	-0.17	-0.37, 0.03	0.10
+DQS	-0.14	-0.37, 0.03	0.19
Non-smokers (n 800)			
*	-0.06	-0.14, 0.01	0.09
+DQS	-0.03	-0.12, 0.06	0.53
<b>Fish <math>\geq</math> once per week</b>			
Smokers (n 114)			
*	-0.52	-0.92, -0.12	0.01
+DQS	-0.49	-0.91, -0.07	0.02
Non-smokers (n 800)			
*	-0.16	-0.30, -0.02	0.03
+DQS	-0.10	-0.25, 0.05	0.17

DQS, diet quality score.

\* Adjusted for age, BMI, Socio-economic Index for Areas scores, physical activity, alcohol consumption and energy intake.

ethyl-EPA attenuated stress- and anxiety-like behaviours in rodents<sup>(35)</sup>. There are also data from two small randomised, placebo-controlled trials in human subjects. Buydens-Branchey & Branchey<sup>(36)</sup> trialled an EPA/DHA supplement *v.* placebo in twenty-four men being treated for substance use. They found a significant reduction in symptoms of anxiety over a 3-month treatment period in the intervention group, and this was maintained for a further 3 months after treatment discontinuation. Another study investigated the impact of DHA supplementation *v.* placebo on fifty-three healthy, non-smoking college students over a 3-month examination period. They reported that measures of stress and aggression increased in the placebo group over this period, whereas those in the intervention group remained stable, suggesting that DHA supplementation may attenuate the stress response in adults<sup>(37)</sup>.

The present findings regarding a non-linear association between DHA consumption and depression and psychological symptoms are concordant with some other observational and intervention studies. Sanchez-Villegas *et al.*<sup>(20)</sup> also failed to detect a linear relationship between LC *n*-3 PUFA consumption and mental illnesses in the Seguimiento Universidad de Navarra (SUN) Cohort Study. In their study, it was the third and fourth quintiles of energy-adjusted EPA and DHA consumption, with median intakes for each quintile of 0.87 and 1.17 g/d, respectively, that demonstrated a reduction in the risk for depression, anxiety and stress over 2 years of follow-up. Those in the highest quintile, with median intakes of 1.89 g/d, showed no reduction in risk. Further support for a biphasic association between DHA and depression is offered by a recent clinical trial, wherein thirty-five depressed adult outpatients with depression were randomised into one of three double-blind dosing arms for 12 weeks. Those receiving 1 g/d of DHA showed the greatest improvement in symptoms (83%), the group receiving 2 g/d improved by 40%, while the group receiving the highest dose showed no improvement<sup>(38)</sup>. In the present study, women with a depressive or anxiety disorder were slightly more likely to take *n*-3 supplements, but this did not explain the observed relationships.

Our observation of an association between frequency of fish intake and psychological symptoms in women is also concordant with many population-based studies previously published. For example, a study of 5689 adults in Finland<sup>(11)</sup> reported that women who rarely ate fish were up to 2.5 times more likely to report depression than regular fish eaters. The risk for suicidal ideation was also increased by 1.5-fold for women who were infrequent fish eaters. However, no such relationships were seen in males. In another cross-sectional Finnish study of 3204 adults, the odds of reporting depressive symptoms were increased by a third for infrequent fish eaters compared to frequent fish eaters<sup>(12)</sup>. When the analyses were split by sex, the association was again significant in women, but not in men. Colangelo *et al.*<sup>(13)</sup> also found an inverse relationship between the dietary intake of fish and *n*-3 PUFA and chronic depression in women, but not men. In contrast, a recent study in adolescents identified a relationship between higher intakes of fish, EPA and DHA and a lower prevalence of depressive symptoms in males, but not females<sup>(39)</sup>. In a community study of 4644 adults in

New Zealand, non-fish consumers scored significantly lower on self-reported mental health measures than fish consumers, and the authors noted that consumption of fish less than once a month appeared to be sufficient for improved self-reported mental health status<sup>(14)</sup>. Similarly, Bountziouka *et al.*<sup>(15)</sup> reported that the consumption of at least one fish meal per week was associated with a reduced likelihood of self-reported depression in older adults. Appleton *et al.*<sup>(16)</sup> also reported inverse associations between the dietary intake of fish and depressed mood in men participating in the Prospective Epidemiological Study of Myocardial Infarction (PRIME), but found that this relationship was confounded by age and social deprivation in another study of population-based adults<sup>(17)</sup>.

The present results suggest that fish consumption may play a role in reducing mental health symptoms. This may be the case or it may be that fish is protective only as a component of a healthy dietary pattern. Most previous studies have not examined diet quality as a confounder in the relationship between fish consumption and depression, and it is plausible to posit that a healthy diet, characterised by a multitude of nutrients that may be important to mental health (e.g. Jacka *et al.*<sup>(22,40–42)</sup>), is the explanatory factor in the relationships observed. In the present study, diet quality explained the association between fish consumption and psychological symptoms in non-smokers, but did not fully explain the relationship in smokers.

The stronger association that we observed between fish consumption and psychological symptoms in smokers is consistent with another study in women. Sontrop *et al.*<sup>(43)</sup> reported an inverse relationship between intakes of *n*-3 PUFA and depression only in pregnant women who were smokers and/or single, but not in other pregnant women. The association of fish or *n*-3 PUFA consumption and mental health is likely to be related to deficiency states only. In support of this contention are previous data indicating a non-linear association between fish consumption and depression; lower intakes of fish being initially associated with depressed mood, but as the intake of fish increases, the relationship with mood is attenuated<sup>(16,17)</sup>. The stronger association we observed between fish intake and psychological symptoms in smokers is suggestive of the idea that in an environment of increased oxidative stress, fish consumption may be particularly protective. Smoking increases oxidative stress and is known to cause lipid peroxidation<sup>(44)</sup>, which may reduce levels of *n*-3 PUFA in tissues. In the present study, the inverse association between fish consumption and psychological symptoms in smokers was particularly clear for those in the lowest quintile of fish consumption (data not shown). On the other hand, a large, longitudinal study of the association among dietary intake of fish, *n*-3 PUFA from fish and low mood, major depression and suicide<sup>(18)</sup> reported no associations between the variables of interest in a population-based survey of 29 133 middle-aged Finnish male smokers.

### Strengths and limitations

These findings are limited by the constraints of a cross-sectional study design, which precludes any determination

regarding the direction of the relationships. Appetite changes and/or biased reporting as a function of psychological status may have influenced the dietary intakes recorded in the present study. Moreover, residual confounding by socio-economic and/or behavioural factors, or unrecognised confounding by factors such as personality traits, are all potential explanations for the present findings. These may also be chance findings, given the number of exposure variables and tests performed. On the other hand, the use of a detailed and validated questionnaire designed to assess vegetable as well as animal sources of PUFA, the assessment of depressive and anxiety disorders using a 'gold standard' tool and the representative nature of our sample<sup>(23)</sup>, which was randomly selected and encompassed the full adult age range, are all important strengths in the present study.

In conclusion, we observed no relationships among the dietary intake of LA, ALA, AA, EPA or DPA and psychological symptoms, depressive and/or anxiety disorders. However, we have reported a non-linear relationship between DHA intake and depressive disorders, a linear relationship between lower consumption of DHA and an increased likelihood of clinically determined anxiety disorders, and a relationship between infrequent fish consumption and increased psychological symptoms in smokers, none of which was confounded by overall dietary quality. These are the first observational data to indicate a role for DHA in anxiety disorders, but suggest that the relationship between DHA and depressive disorders may be non-linear. They also suggest that regular fish consumption may be of particular importance to smokers. Further research should now examine the potential of DHA as a treatment strategy in anxiety and focus on determining the optimal level of DHA intake in the prevention and treatment of depression.

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content and final approval of the version for publication. R. D. performed data collation, critical revision for important intellectual content and final approval of the version for publication. M. B. carried out conception and design, interpretation of data, critical revision for important intellectual content and final approval of the version for publication. All authors had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

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