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Research paper

Dietary n-3 PUFA, fish consumption and depression: A systematic review and meta-analysis of observational studies

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ABSTRACT

Background: Fish consumption and n-3 polyunsaturated fatty acids (PUFA) have been hypothesized to exert preventive effects toward depressive disorders, but findings are contrasting. We aimed to systematically review and perform meta-analysis of results from observational studies exploring the association between fish, n-3 PUFA dietary intake, and depression.
Methods: A search on the main bibliographic source of the observational studies up to August 2015 was performed. Random-effects models of the highest *versus* the lowest (reference) category of exposure and dose-response meta-analysis were performed.
Results: A total of 31 studies including 255,076 individuals and over 20,000 cases of depression, were examined. Analysis of 21 datasets investigating relation between fish consumption and depression resulted in significant reduced risk (RR=0.78, 95% CI: 0.69, 0.89), with a linear dose-response despite with moderate heterogeneity. Pooled risk estimates of depression for extreme categories of both total n-3 PUFA and fish-derived n-3 PUFA [eicosapentaenoic acid (EPA)+docosahexaenoic acid (DHA)] resulted in decreased risk for the highest compared with the lowest intake (RR=0.78, 95% CI: 0.67, 0.92 and RR=0.82, 95% CI: 0.73, 0.92, respectively) and dose-response analysis revealed a J-shaped association with a peak decreased risk for 1.8 g/d intake of n-3 PUFA (RR=0.30, 95% CI: 0.09, 0.98).
Limitation: Design of the studies included and confounding due to lack adjustment for certain variables may exist.
Conclusions: The present analysis supports the hypothesis that dietary n-3 PUFA intake are associated with lower risk of depression.

1. Introduction

Over the last four decades, polyunsaturated fatty acids (PUFA) have been studied in relation to prevention of cardiovascular diseases (CVD) (Sanchez-Villegas and Martinez-Gonzalez, 2013). The highest representative compounds consumed by humans belong to the n-3 and n-6 family of PUFA, including alpha-linolenic acid (ALA) and linoleic acid (LA), respectively (Grosso et al., 2014a). Once consumed in the diet, LA undergoes to transformation in arachidonic acid (AA), which is precursor of pro-inflammatory cytokines, whereas ALA is converted into eicosapentaenoic acid (EPA), with a subsequent elongation to docosahexaenoic acid (DHA). EPA and DHA may also be consumed directly through ingestion of fish and seafood. The beneficial effect of n-3 PUFA is supposed to depend on their capacity to positively modulate the immune and inflammatory response (Gil, 2002; Tapiero et al., 2002), as they demonstrated a certain efficacy in preventing illnesses with an inflammatory component (Parletta et al., 2013). An emerging body of data indicates n-3 PUFA as potential candidates in the prevention and treatment of psychiatric diseases involving inflammatory processes, such as depressive disorders (Bourre, 2007). Ecological studies showed that dietary intakes of fish correlate with lower prevalence of major depression (Hibbeln, 1998), bipolar disorder (Noaghiul and Hibbeln, 2003), and post-partum depression (Hibbeln, 2002). These findings suggested that cross-national variations in n-3 PUFA intake contained in fish are inversely correlated with the prevalence of depression.

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The potential benefits of n-3 PUFA intake in preventing or treating psychiatric illnesses, such as depressive disorders, are biologically plausible. Major depression shares certain pathophysiological mechanisms with CVD, such as increased production of pro-inflammatory cytokines, endothelial dysfunction, and elevations in plasma homocysteine levels (Hepgul et al., 2010). Several studies have shown a positive correlation between the severity of the symptoms of depression and the increase in the inflammatory status (Maes et al., 2009). Major depression has been recently considered secondary to a systemic inflammatory disorder in which pro-inflammatory cytokines alter serotonin metabolism, reduce synaptic plasticity, and increase the risk of developing diseases associated with an inflammatory state (Caraci et al., 2010; Huffman et al., 2013; Maes et al., 2009). According to this scenario, the anti-inflammatory capacity of n-3 PUFA has been hypothesized to play a central role in counteracting inflammatory processes occurring in depression (Parletta et al., 2013). Another possible mechanism may depend on n-3 PUFA neuro-endocrine metabolism, release, uptake, and receptor action (Hibbeln et al., 1998). N-3 PUFA have been shown to interact with serotonin metabolism by facilitating its release by inhibiting the formation of E2-series prostaglandins and increasing membrane fluidity (Patrick and Ames, 2015). Their positive effects on depression may also depend on their physiological abundant content in the human nervous system and their involvement in neurogenesis and neuroplasticity (Bourre, 2004).

There is evidence that depressed patients have decreased content of n-3 PUFA in plasma and erythrocyte membrane, supporting the mechanistic links between n-3 PUFA deficiency and increased risk of depression (De Vriese et al., 2003; Edwards et al., 1998; Peet et al., 1998). A number of cross-sectional and prospective investigations have been performed to test the potential association between fish consumption, n-3 PUFA dietary intake and depression, but findings are contrasting (Giles et al., 2013). The use of n-3 PUFA supplements as add-on therapy for major depression (in addition to first and second generation antidepressant drugs) appears promising but observational studies analyzing free-living populations did not yield to strong conclusions on the potential protective role of n-3 PUFA in preventing depressive disorders (Grosso et al., 2014b). Indeed, it is still unclear whether a biological response to dietary n-3 PUFA can be obtained in a dose-dependent manner with clinically relevant effects in the general population. Thus, the main aim of this study was to systematically review observational studies exploring the association between fish, n-3 PUFA dietary consumption and depression. A meta-analysis of risk estimates to calculate effect-size and eventually define the dose-response effect was performed.

2. Methods

2.1. Search strategy and selection of the studies

A comprehensive search on MEDLINE, EMBASE, PsycInfo, and the Cochrane Database of Systematic Reviews of all observational studies evaluating the effects of n-3 PUFA on depression in cohort of individuals published up to August 2014 was performed. Articles of potential interest were identified using the following search terms: “omega-3”, “polyunsaturated fatty acids”, “PUFA”, “EPA”, “DHA”, “alpha linolenic acid”, “linoleic acid”, combined with the following terms: “depression”, “depressive disorder”, “depressed mood”, combined with “cohort”, “prospective”, and “cross-sectional”. Inclusion criteria were report of risk measures [odds ratios (ORs) or hazard ratios (HRs)] for fish, total n-3 PUFA, EPA, DHA, ALA or n-3: n-6 PUFA ratio intake and depression. For dose-response meta-analysis, studies had to provide a quantitative measure of exposure for at least three categories with the estimates of ORs or HRs and 95% confidence interval (CI), category-specific or total number of either cases or non-cases or person-years. The reference list of the relevant reports was also inspected to identify any additional study not previously included. Exclusion criteria were the following: i) studies with different design; ii) studies considering depression as secondary outcome. Only articles in English were included.

2.2. Data extraction and study quality

Data were abstracted from each identified trial by GG and AM using a standard data abstraction form. This process was independently performed by the two researchers and discordances were resolved through discussion. Information from each study including author, year of publication, study design, participant characteristics, depression and fish/n-3 PUFA consumption assessment methodology, number of cases, dose for each category of exposure, adjustments, and main results including ORs, HRs, and 95% confidence intervals (CIs) were extracted and tabulated for comparative analysis. When studies reported n-3 PUFA intake as percentage of total energy intake, the intake was estimated accordingly.

The quality of each study was assessed following the principles of the Newcastle-Ottawa Quality Assessment Scale (Wells et al., 1999), consisting of 3 domains of quality as follows: selection (4 points), comparability (2 points), and outcome (3 points) for a total score of 9 points (9 representing the highest quality). Studies scoring 7–9 points, 3–6 points, and 0–3 points were identified as high, moderate, and low quality, respectively.

2.3. Statistical analysis

In this meta-analysis, ORs and HRs were deemed equivalent to relative risks (RRs) (Greenland, 1987). ORs/HRs with 95% CI for all categories of exposure were extracted for the analysis and random-effects models were used to calculate pooled RR with 95% CIs for highest *vs*. lowest (reference) category of exposure. The risk estimate from the most fully adjusted models in the analysis of the pooled RR was used. When the estimated risk presented in a study was in relation to any other consumption group than "the smallest", these were rescaled in relation to the smallest consumption category by the authors using the approach set out in Hamling et al. *(*Hamling et al., 2008*)*. Briefly, the standard errors and confidence intervals were re-calculated consistently for each rescaled risk estimate based on the adjusted results presented in the papers. The same methodology was used in order to combine categories of exposure whether more than five categories were used in a study. Heterogeneity was assessed by using the Q test and I^2 statistic. The level of significance for the Q test was defined as $P < 0.10$. The I^2 statistic represented the amount of total variation that could be attributed to heterogeneity. I^2 values $\leq 25\%$, $\leq 50\%$, $\leq 75\%$, and $> 75\%$ indicated no, small, moderate, and significant heterogeneity, respectively. A sensitivity analysis by exclusion of one study at a time was performed to assess the stability of results and potential sources of heterogeneity. Subgroup analyses were also performed to check for potential source of heterogeneity according to study design, study quality, gender, study location, adjustment for dietary and socio-economic variables. Publication bias was evaluated by a visual investigation of funnel plots for potential asymmetry.

Data on the amount of fish/n-3 PUFA intake, distributions of cases and person-years (when available), and ORs/HRs with 95% CIs for ≥ 3 exposure categories were extracted. The median or mean intake of fish/n-3 PUFA in each category was assigned to the corresponding OR/HR with the 95% CI for each study. When fish/n-3

PUFA consumption was reported by ranges of intake, the midpoint of the range was used. When the highest category was open ended, we assumed the width of the category to be the same as the adjacent category. When the lowest category was open ended, we set the lower boundary to zero. These data were used to perform a two-stage dose-response analysis to examine a potential non-linear relationship between the variables of interest and depression. The dose-response analysis was modeled by using restricted cubic splines with 3 knots at fixed percentiles (25%, 50%, and 75%) of the distribution (Orsini et al., 2012). In a first stage, a restricted cubic spline model with 2 spline transformations (3 knots minus 1) was fitted taking into account the correlation within each set of retrieved RRs. In the second stage, we combined the 2 regression coefficients and the variance/covariance matrices that had been

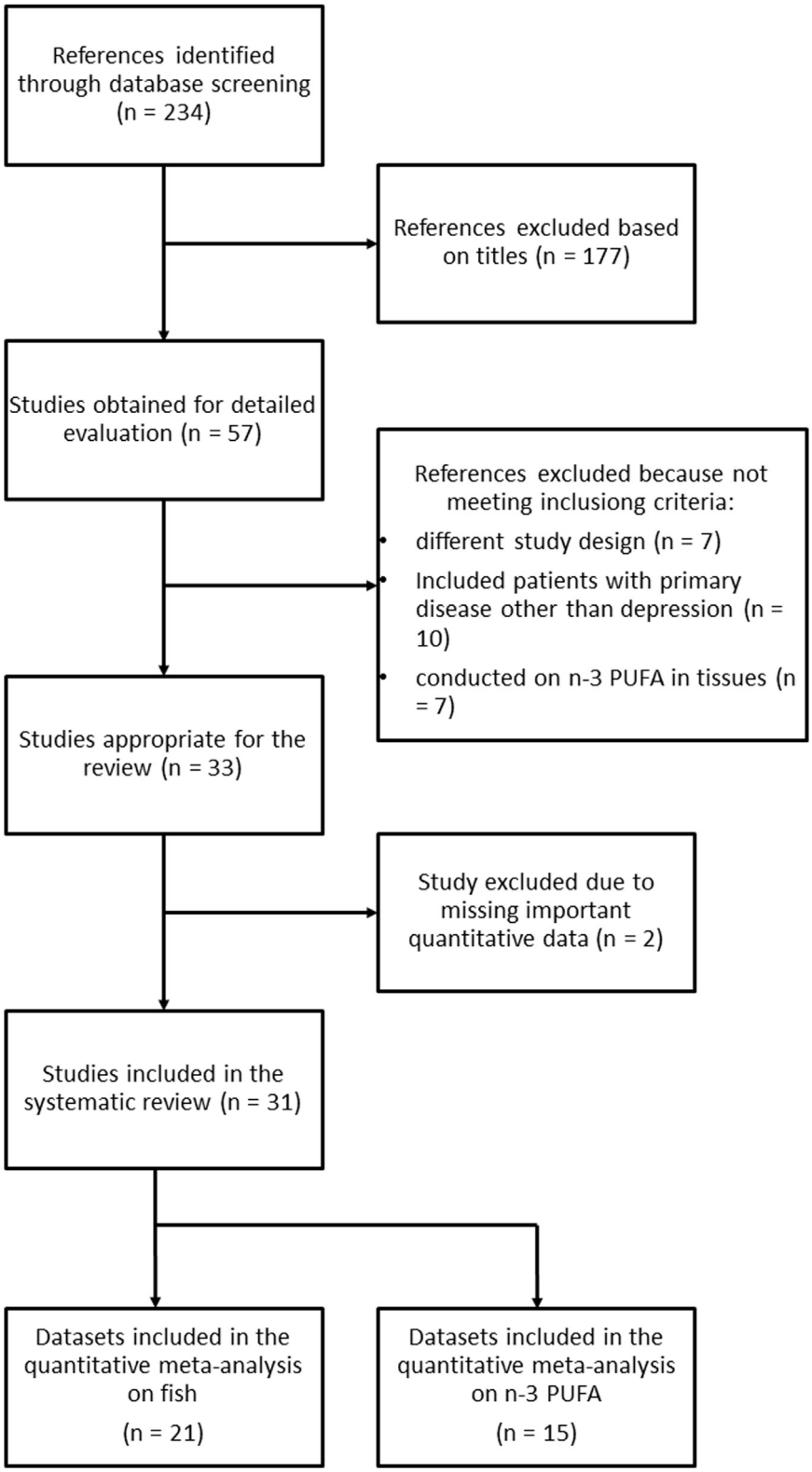

Fig. 1. Flowchart indicating the results of the systematic review of relevant studies exploring association between fish and n-3 PUFA dietary intake and depression.

estimated within each study, using the multivariate extension of the method of moments in a multivariate random-effects meta-analysis. All analyses were performed with R version 3.0.3 software (Development Core Team).

3. Results

3.1. Study characteristics

The process of identification and inclusion of studies is summarized in Fig. 1. Among the 232 articles retrieved, observational studies were identified and screened by reading the abstract and, when necessary, the full text. Twenty-six out of the 57 articles considered potentially relevant were excluded and not assessed further for the following reasons: 2 reported insufficient statistics or did not present crucial data, 7 were conducted on n-3 PUFA in tissues, 7 had different study design, 10 were conducted on individuals with primary disease different than depression. This process led to a final number of 31 studies (Albanese et al., 2012; Appleton et al., 2007a, 2007b; Astorg et al., 2008; Barberger-Gateau et al., 2005; Beydoun et al., 2013, 2015; Bountziouka et al., 2009; Chrysohoou et al., 2011; Colangelo et al., 2009; da Rocha and Kac, 2012; Daley et al., 2014; Golding et al., 2009; Hakkarainen et al., 2004; Jacka et al., 2013; Kamphuis et al., 2006; Kesse-Guyot et al., 2012; Kyrozis et al., 2009; Li et al., 2011; Lucas et al., 2011; Miyake et al., 2006; Murakami et al., 2010, 2008; Oddy et al., 2011; Sanchez-Villegas et al., 2007, 2009; Sontrop et al., 2008; Strom et al., 2009; Suominen-Taipale et al., 2010; Tanskanen et al., 2001; Timonen et al., 2004) considered in this systematic review, including 255,076 individuals and over 20,000 cases of depression.

The most relevant characteristics of the studies included in this systematic review are reported in Table 1. Eight studies explored the association of both fish and n-3 PUFA dietary consumption and depression (Astorg et al., 2008; Colangelo et al., 2009; Hakkarainen et al., 2004; Lucas et al., 2011; Miyake et al., 2006; Murakami et al., 2010; Sontrop et al., 2008; Strom et al., 2009), 11 were focused only on fish consumption (Albanese et al., 2012; Appleton et al., 2007b; Barberger-Gateau et al., 2005; Bountziouka et al., 2009; Chrysohoou et al., 2011; Kyrozis et al., 2009; Li et al., 2011; Sanchez-Villegas et al., 2009; Suominen-Taipale et al., 2010; Tanskanen et al., 2001; Timonen et al., 2004), 9 considered only n-3 PUFA intake (Appleton et al., 2007a; Beydoun et al., 2013, 2015; Daley et al., 2014; Golding et al., 2009; Jacka et al., 2013; Kamphuis et al., 2006; Kesse-Guyot et al., 2012; Murakami et al., 2008; Oddy et al., 2011; Sanchez-Villegas et al., 2007), and 1 only the n-6: n-3 PUFA ratio (da Rocha and Kac, 2012). Thirteen studies (Albanese et al., 2012; Appleton et al., 2007a; Barberger-Gateau et al., 2005; Beydoun et al., 2013; Bountziouka et al., 2009; Daley et al., 2014; Golding et al., 2009; Kamphuis et al., 2006; Murakami et al., 2010, 2008; Sontrop et al., 2008; Suominen-Taipale et al., 2010; Tanskanen et al., 2001) adopted a cross-sectional design, 15 were prospective studies (Appleton et al., 2007b; Astorg et al., 2008; Beydoun et al., 2015; Colangelo et al., 2009; da Rocha and Kac, 2012; Hakkarainen et al., 2004; Jacka et al., 2013; Kyrozis et al., 2009; Li et al., 2011; Lucas et al., 2011; Miyake et al., 2006; Sanchez-Villegas et al., 2009, 2007; Strom et al., 2009; Timonen et al., 2004), and 2 presented data with both designs (Kesse-Guyot et al., 2012; Oddy et al., 2011). The duration of follow-up for the prospective studies ranged from 2 to 30 years. Overall, 8 studies (Astorg et al., 2008; Beydoun et al., 2013, 2015; Hakkarainen et al., 2004; Kesse-Guyot et al., 2012; Lucas et al., 2011; Miyake et al., 2006; Strom et al., 2009) scored high quality.

Participant characteristics and the methods for assessing consumption and classification of n-3 PUFA consumption and foods varied among studies. Most of the studies were conducted on general population (Appleton et al., 2007a, 2007b; Astorg et al., 2008; Beydoun et al., 2013, 2015; Colangelo et al., 2009; Hakkarainen et al., 2004; Kesse-Guyot et al., 2012; Li et al., 2011; Sanchez-Villegas et al., 2007; Suominen-Taipale et al., 2010; Tanskanen et al., 2001; Timonen et al., 2004), 2 on community dwellers (Albanese et al., 2012; Barberger-Gateau et al., 2005), 3 on health professionals or employee (Lucas et al., 2011; Murakami et al., 2008; Suominen-Taipale et al., 2010), 5 on women during or after pregnancy (da Rocha and Kac, 2012; Golding et al., 2009; Miyake et al., 2006; Sontrop et al., 2008; Strom et al., 2009), 2 on adolescents (Murakami et al., 2010; Oddy et al., 2011), and 3 on elderly (60+ years) individuals (Bountziouka et al., 2009; Kamphuis et al., 2006; Kyrozis et al., 2009). Dietary assessment was performed with a validated food frequency questionnaire (FFQ) in almost all studies, with the exception of 4 studies (Astorg et al., 2008; Beydoun et al., 2013, 2015; Kesse-Guyot et al., 2012) that used 24-h recalls, and one study (Albanese et al., 2012) using specific assessment questions. The majority of studies separated individuals into categories of exposure (quantiles) based on daily amount of fish consumed or n-3 PUFA intake whereas 7 studies (Appleton et al., 2007a, 2007b; Bountziouka et al., 2009; Daley et al., 2014; Kyrozis et al., 2009; Lucas et al., 2011; Oddy et al., 2011) considered fish and n-3 PUFA intakes as continuous variables. Most of the studies identified cases of depression according the cut-off points of the scores respectively used, 5 accounting clinical diagnosis, hospitalization, or medicament prescription (Colangelo et al., 2009; Hakkarainen et al., 2004; Jacka et al., 2013; Lucas et al., 2011; Timonen et al., 2004), and 7 used values of the score as a continuous variable for the analyses (Appleton et al., 2007a, 2007b; Beydoun et al., 2015; Bountziouka et al., 2009; Kyrozis et al., 2009; Lucas et al., 2011; Oddy et al., 2011).

The amount of dietary n-3 PUFA and fish intake varied with a great extent across studies, with a general higher consumption in all studies conducted in Japan (Miyake et al., 2006; Murakami et al., 2008, 2010), reporting almost 2–3 g/d or 2% of energy for n-3 PUFA and 70 g/d of fish intakes in the highest quantiles of consumption. In contrast, the lowest intakes among the highest quantiles of consumption were reported in studies conducted in Germany (Kamphuis et al., 2006) and England (Golding et al., 2009). All studies adjusted analysis for confounders, but number and type of potential confounders used for statistical adjustment varied between studies, most of them including age, gender (when both sexes were included), smoking, and education. Among other confounders, most of the studies adjusted for occupational, social or poverty-income status while only a minority adjusted for other dietary variables.

3.2. Fish consumption and depression

Eighteen studies were exploring the possible association between fish consumption and depression. Five (Barberger-Gateau et al., 2005; Bountziouka et al., 2009; Murakami et al., 2010; Suominen-Taipale et al., 2010; Tanskanen et al., 2001) out of 7 cross-sectional and 6 (Astorg et al., 2008; Kyrozis et al., 2009; Li et al., 2011; Miyake et al., 2006; Strom et al., 2009; Timonen et al., 2004) out of 11 prospective studies reported a significant relation. Included studies involved 107,098 men and women of various ages, followed in prospective studies up to 13 years. Two studies conducted in Greece (Bountziouka et al., 2009; Kyrozis et al., 2009) and one in Northern Ireland (Appleton et al., 2007b) reported a linear association between fish intake and scores of depression.

Fifteen studies including 21 datasets were used for the quantitative analysis of the extreme categories of fish consumption and depression (Fig. 2). Pooled analysis of the highest vs. the lowest (reference) fish consumption category resulted in a 22% decreased risk of depression (RR =0.78, 95% CI: 0.69, 0.89), with evidence of

Table 1
Characteristics and main findings of the observational studies conducted on fish and n-3 PUFA dietary intake and depression.

Author, year; study design (follow-up)	Country (cohort name)	Dietary assessment	Depression assessment	Participants characteristics	Adjustment for confounders	Main findings	Study quality
Tanskanen, 2001; cross-sectional (25)	Finland	FFQ	BDI	General population; n =3204; age 25–64 y	Age, marital status, occupation, smoking status, physical activity, BMI, alcohol intake, coffee intake, educational level, serum cholesterol level.	Fish (rare vs. regular eaters), OR=1.31 (95% CI: 1.10, 1.56)	Moderate
Hakkarainen et al., 2004; Prospective (5–8 y) (26)	Finland (ATBC study)	FFQ	Hospital treatment	General population; n=29,133; age 50–69 y	Age, body mass index, energy intake, serum total cholesterol level, high-density lipoprotein cholesterol level, consumption of alcohol, education, marriage, self-reported depression, self-reported anxiety, and smoking.	Fish (highest vs. lowest tertile), OR=0.97 (95% CI: 0.70, 1.33) n-3 PUFA (highest vs. lowest tertile), OR=0.96 (95% CI: 0.70, 1.30)	High
Timonen et al., 2004; Prospective (31 y) (27)	Finland (Northern Finland 1966 Birth Cohort)	FFQ	Hopkins Symptom Check List-25 subscale and diagnosis by medical doctor	General population; n=5689; age < 31 y	Alcohol intake, smoking, physical inactivity, and marital status.	Fish (rare vs. regular eaters), men: OR=0.8 (95% CI: 0.4, 1.6); women: OR 2.4 (95% CI: 1.4, 4.2)	Moderate
Barberger-Gateau et al., 2005; Cross-sectional (28)	France (Three-City Study)	FFQ	CES-D (depression ≥ 16)	Community dwellers; n=9280; age 64+ y	Age, sex, education, and city.	Fish (> once a week vs. < once a week), OR=0.63 (95% CI: 0.52, 0.75)	Moderate
Kamphuis et al., 2006; Cross-sectional (29)	German (Zutphen Elderly Study)	FFQ	Self-rating Depression Scale	Elderly general population; n=332; age 70–90 y	Age, years of education, BMI, smoking status, alcohol consumption, systolic blood pressure, physical activity, living alone	n-3 PUFA (highest vs. lowest category), OR=0.46 (95% CI: 0.22, 0.95), P for trend=0.04	Moderate
Miyake et al., 2006; Prospective (2–9 m post-partum) (30)	Japan (Osaka Maternal and Child Health Study)	FFQ	EPDS (depression ≥ 9)	Pregnant women; n=865; age < 32 y	Age, gestation, parity, cigarette smoking, family structure, family income, education, changes in diet in the previous month, season when data at baseline were collected, BMI, time of delivery before the second survey, medical problems in pregnancy, baby's sex and baby's birth weight.	Fish (highest vs. lowest category), OR=0.89 (95% CI: 0.50, 1.59), P for trend=0.37 n-3 PUFA (highest vs. lowest category), OR=0.90 (95% CI: 0.53, 1.53), P for trend=0.61 n-3/n-6 PUFA ratio, (highest vs. lowest category), OR=0.97 (95% CI: 0.55, 1.68), P for trend=0.95	High
Appleton et al., 2007a; Cross-sectional (31)	UK	FFQ	DASS-21	General population; n=2982; age 25–65 y	Age, gender, Index of Multiple Deprivation score, date of questionnaire completion.	n-3 PUFA (linear component), Beta=0.08 (95% CI: −0.07, 0.23)	Moderate
Appleton et al., 2007b; Prospective (5 y) (32)	Northern Ireland and France (PRIME cohort)	FFQ	Welsh Pure Depression subscale of the Minnesota Multiphasic Personality Inventory	General population (men); n=10,602; age 50–59 y	All diet and demographic variables.	Fish (linear term), Northern Ireland: Beta=−0.09 (95% CI: −2.25, −0.01), P=0.05; France: Beta=−0.14 (95% CI: −2.73, −1.17), P < 0.01	Moderate
Sanchez-Villegas et al., 2007; Prospective (2 y) (33)	Spain (SUN cohort)	FFQ	Self-reported physician diagnosis of depression, anxiety or stress or use of antidepressant medication or tranquilizers	General population; n=7903; age 38 y (mean)	Age, gender, incapacitating disease, energy intake, physical activity during leasure time, and change in physical activity since baseline.	n-3 PUFA (highest vs. lowest category), OR=1.04 (95% CI: 0.78, 1.40), P for trend=0.376	Moderate
Astorg et al., 2008; Prospective (2 y) (34)	France (SUVIMAX)	24-h recall	Antidepressant or lithium prescription	General population; n=3748; age 35–60 y	Age, sex, intervention group, family status, education level, and tobacco use.	Fish (highest vs. lowest category), OR=0.71 (95% CI: 0.52, 0.97), P for trend=0.029	High
Murakami et al., 2008; Cross-sectional (35)	Japan	FFQ	CES-D (depression ≥ 16)	Municipal employees; n=517; age 21–67 y	Age, BMI, work place, marital status, occupational physical activity, leisure-time physical activity, smoking status, alcohol drinking, and job stress score.	n-3 PUFA (highest vs. lowest category), men: OR=0.58 (95% CI: 0.28, 1.19) , P for trend=0.13; women: OR=1.46 (95% CI: 0.57, 3.76), P for trend=0.54	Moderate
Sontrop et al., 2008; Cross-sectional (36)	Canada (Prenatal Health Project)	FFQ	CES-D (depression ≥ 16)	Pregnant women (10- and 22-week gestation); n=2394; age 21–35 y	Socio-demographic, health and lifestyle variables.	Fish (1/week vs. < 1/week), Beta=−0.2 (95% CI: −0.9, 0.4) n-3 PUFA (85 mg/day vs. < 85 mg/day), Beta=0.1 (95% CI: −0.6, 0.8)	High

Table 1 (*continued*)

Author, year; study design (follow-up)	Country (cohort name)	Dietary assessment	Depression assessment	Participants characteristics	Adjustment for confounders	Main findings	Study quality
Golding et al., 2009; Cross-sectional (37)	England (Avon Longitudinal Study of Parents and Children)	FFQ	EPDS (depression ≥ 13)	Women (32 weeks' gestation); n=14,541; age not specified	Energy intake, maternal age, maternal education, maternal smoking, maternal ethnic background, housing tenure, crowding, childhood life events, recent life events, chronic stress, parity, and outcome of immediately preceding pregnancy.	n-3 PUFA (none vs. > 1.5 g/week), OR=1.54 (95% CI: 1.25, 1.89), P for trend < 0.001	Moderate
Strom et al., 2009; Prospective (1 y post-partum) (38)	Denmark (Danish National Birth Cohort)	FFQ	Post-partum depression hospital admission or medicament prescription	Women; n=54,202; age 25–40 y	Total energy intake, prepregnant BMI, maternal age, parity, alcohol intake, smoking, occupation, education, homeownership, marital status, social support, and history of previous depression.	Fish (lowest vs. highest category), post-partum depression hospital admission: OR=0.82 (95% CI: 0.42, 1.64), P for trend=0.50; post-partum depression medicament prescription: OR=1.46 (95% CI: 1.12, 1.90) P for trend=0.04 n-3 PUFA (lowest vs. highest category), post-partum depression hospital admission: OR=0.96 (95% CI: 0.51, 1.78), P for trend=0.38; post-partum depression medicament prescription: OR=1.24 (95% CI: 0.96, 1.61) P for trend=0.33	High
Bountziouka et al., 2009; Cross-sectional (39)	Greece and Cyprus (MEDIS study)	FFQ	GDS	Elderly general population; n=1190; age 65+ y	Not specified	Fish (linear), Beta= −0.529 (95% CI: −0.45, −0.73)	Moderate
Colangelo et al., 2009; Prospective (10 y) (40)	US (Coronary Artery Risk Development in Young Adults study [CARDIA])	FFQ	CES-D (depression ≥ 16)	General population (women); n=3317; age 24–42 y	Age, race, gender, educational level, BMI, smoking status, alcohol intake, total physical activity, and marital status.	Fish (highest vs. lowest category), men: OR=0.89 (95% CI: 0.62, 1.28), P for trend=0.96; women: OR=0.75 (95% CI: 0.55, 1.01), P for trend=0.02 n-3 PUFA (highest vs. lowest category), men: OR=0.91 (95% 0.64, 1.30), P for trend=0.93; women: OR=0.71 (95% 0.52, 0.95), P for trend=0.001	Moderate
Kyrozis et al., 2009; Prospective (6–13 y) (41)	Greece (EPIC-Greece)	FFQ	GDS	Elderly general population; n=610; age 60+ y	Gender, age, marital status, years of education, height, BMI, physical activity, smoking, alcohol intake, coffee intake, energy daily intake, hypertension at baseline, diabetes at baseline, Mediterranean diet adherence, cancer at follow-up, and cardiac disease.	Fish (linear), Beta= −0.08 (95% CI: −0.30, 0.15), P=0.513	Moderate
Sanchez-Villegas, 2009; Prospective (4.4 y) (42)	Spain (SUN cohort)	FFQ	Self-reported physician diagnosis of depression, anxiety or stress or use of antidepressant medication or tranquilizers	General population; n=10,094; age 38 y (mean)	Sex, age, smoking status, BMI, physical activity during leisure-time, and employment status.	Fish (highest vs. lowest category), HR=0.85 (95% CI: 0.64, 1.13), P for trend=0.31	Moderate
Murakami et al., 2010; Cross-sectional (43)	Japan	FFQ	CES-D (depression ≥ 16)	Adolescents (school students); n=6517; age 12–15 y	Age, habitual exercise, paternal educational level, and maternal educational level.	Fish (highest vs. lowest category), men: OR=0.73 (95% CI: 0.55, 0.97), P for trend=0.002; women: OR=1.01 (95% CI: 0.80, 1.28), P for trend=0.79 n-3 PUFA (highest vs. lowest category), men: OR=0.72 (95% CI: 0.55, 0.98), P for trend=0.08; women: OR=1.05 (95% CI: 0.83, 1.33), P for trend=0.43	High

Suominen-Taipale et al., 2010; Cross-sectional (44)	Finland (Health 2000 Survey)	FFQ	M-CIDI	General population; n=5492; age 45–74 y	Age, total energy intake for fish consumption, BMI, level of education, marital status, smoking history, physical activity, and alcohol intake.	Fish (highest vs. lowest category), OR=0.6 (95% CI: 0.3, 0.9), P for trend=0.03	Moderate
Suominen-Taipale et al., 2010; Cross-sectional (44)	Finland (Fishermen Study)	FFQ	CIDI-SF	Fishermen with their families; n=1265; age not specified	Age, total energy intake for fish consumption, BMI, level of education, marital status, smoking history, physical activity, and alcohol intake.	Fish (highest vs. lowest category), OR=0.1 (95% CI: 0.02, 0.5), P for trend=0.002	Moderate
Chrysohoou, 2011; Cross-sectional (45)	Greece (IKARIA study)	FFQ	GDS (self-report)	Elderly general population; n=673; age >65 y	Not specified.	Fish (highest vs. lowest category), OR=0.34 (0.19, 0.61)	Moderate
Li et al., 2011; Prospective (10.6 y) (46)	US (First National Health and Nutrition Examination Survey Follow-up Study)	FFQ	CES-D (depression ≥22)	General population; n=5068; age 25–74 y	Age, race/ethnicity, education attainment, family income level, marital status, types of residence area, occupation, employment, BMI, alcohol drinking, cigarette smoking, serum total cholesterol, total dietary energy intake, saturated fatty intake, fruit and vegetable intake, health status.	Fish (<1/week vs. >1 week), men: OR=2.08 (95% CI: 1.08, 4.09), P for trend=0.03; women: OR=1.15 (95% CI: 0.83, 1.59), P for trend=0.40	Moderate
Lucas et al., 2011; Prospective (10 y) (47)	US (Nurses' Health Study)	FFQ	Physician-diagnosed depression and regular antidepressant medication use	Nurses (women); n=54,632; age 50–77 y	Age, time interval of the study, hormonal status, race, obesity, smoking status, physical activity, diagnosis of diabetes, cancer, myocardial infarction, multivitamin use, average intake of energy, protein, trans fatty acids, saturated fatty acids, monounsaturated fatty acids, alcohol, and n-3 and n-6-PUFA.	Fish (>5 times/month vs. < 1 time/month), RR=1.07 (95% CI: 0.74, 1.55) n-3 (0.3 g/d increment), RR=0.99 (95% CI: 0.88, 1.10) ALA (0.5 g/d increment), RR=0.81 (95% CI: 0.69, 0.65) n-3: n-6 PUFA ratio (increase of 0.1 U), RR=0.74 (95% CI: 0.61, 0.90)	High
Oddy et al., 2011; Cross-sectional (48)	Australia [Western Australian Pregnancy Cohort (Raine) Study]	FFQ	BDI-Y	Adolescents; n=1407; age 14 y	BMI, physical activity level, and socioeconomic status.	n-3 (linear), beta −0.03 (95% CI: −0.23, 0.17), P=0.76	Moderate
Oddy et al., 2011; Prospective (3 y) (48)	Australia [Western Australian Pregnancy Cohort (Raine) Study]	FFQ	BDI-Y	Adolescents; n=995; age 17 y	BMI, physical activity level, and socioeconomic status.	n-3 (linear), beta −0.14 (95% CI: −0.40, 0.18), P=0.29	Moderate
Da Rocha, 2012; Prospective (30 d postpartum) (49)	Brazil	FFQ	EPDS (depression ≥11)	Pregnant women (between 8th and 13th week of gestation); n=106; age 18–41 y	Age, schooling, pre-pregnancy BMI, time elapsed since delivery, lipids consumption.	n-6: n-3 PUFA ratio (>9:1 vs. <9:1), HR: 2.50 (95% CI: 1.21, 5.14), P=0.013	Moderate
Kesse-Guyot et al., 2012; Cross-sectional (50)	France (SUVIMAX)	24-h recall	CES-D (depression >15)	General population; n=2744; age 35–60 y	Age, gender, physical activity, educational level, intervention group, energy intake, marital status, number of 24-h recalls, alcohol consumption, BMI, saturated fatty acids intake, vegetable and fruit consumption, n-3 and n-6 PUFA.	n-3 PUFA (highest vs. lowest category), OR=0.74 (95% CI: 0.58, 0.95), P for trend <0.001 n-6/n-3 PUFA ratio (highest vs. lowest quartile), OR=1.14 (95% CI: 0.90, 1.43)	High
Kesse-Guyot et al., 2012; Prospective (13 y) (50)	France (SUVIMAX)	24-h recall	CES-D (depression >15)	General population; n=1235; age 35–60 y	Age, gender, physical activity, educational level, intervention group, energy intake, marital status, number of 24-h recalls, alcohol consumption, BMI, saturated fatty acids intake, vegetable and fruit consumption, n-3 and n-6 PUFA.	n-3 PUFA (highest vs. lowest category), OR=1.02 (95% CI: 0.60, 1.75), P for trend <0.76 n-6: n-3 PUFA ratio (highest vs. lowest category), OR=0.98 (95% CI: 0.58, 1.65)	High
Albanese et al., 2012; Cross-sectional (51)	Multicenter (10/66 research program)	Standardized questions	ICD-10 depressive episode	Community dwellers; n=14,926; age 65+ y	Age, gender, educational level, number of household assets, marital status, self-reported diagnosed diabetes, coronary heart disease and stroke, number of physical illnesses, overall cognitive status, weekly meat intake, fruits and vegetables consumption, alcohol intake, physical activity.	Fish, never: OR 0.93 (95% CI: 0.78, 1.10); some days: OR=1 (reference); most days: OR=1.07 (95% CI: 0.85, 1.86)	Moderate

Table 1 (*continued*)

Author, year; study design (follow-up)	Country (cohort name)	Dietary assessment	Depression assessment	Participants characteristics	Adjustment for confounders	Main findings	Study quality
Jacka et al., 2012; Prospective (10 y) (52)	Australia (Geelong Osteoporosis Study)	FFQ	Structured Clinical Interview for DSM-IV-TR	General population (women); n=935; age 20–94 y	Energy intake and diet quality score.	EPA (highest vs. lowest category), OR=1.31 (95% CI: 1.64, 2.69) DHA (highest vs. lowest category), OR=1.44 (95% CI: 0.73, 2.83)	Moderate
Beydoun et al., 2013; Cross-sectional (53)	US (Healthy Aging in Neighborhoods of Diversity across the Life Span [HANDLS] study)	24-h recall	CES-D (depression ≥ 16)	General population; n=1746; age 30–64 y	Age, race/ethnicity, marital status, education, poverty-income ratio, smoking and drug use status, measured BMI, selected nutrients and total energy intake.	n-3 PUFA (highest vs. lowest category), men: OR=1.40 (95% CI: 0.66, 2.97); women: OR=0.51 (95% CI: 0.27, 0.95) n-3/n-6 ratio PUFA (highest vs. lowest category), men: OR=1.24 (95% CI: 0.60, 2.56); women: OR=0.47 (95% CI: 0.27, 0.83)	High
Daley et al., 2014; Cross-sectional (54)	Australia (Australian Longitudinal Study on Women's Health [ALSWH] Young Cohort Survey 3)	FFQ	CES-D (depression ≥ 10)	General population (women); n=7635; age 25–30 y	BMI, energy intake, physical activity, chronic illnesses, alcohol intake, education, drug use, smoking status, pregnancy status, abuse, area of residence, managing on income, marital status, major life events, symptoms, depression medications.	EPA (linear), OR=1.31 (95% CI: 0.75, 2.34) DHA (linear), OR=1.20 (95% CI: 0.89, 1.61) ALA (linear), OR=0.77 (95% CI: 0.60, 0.90)	Moderate
Beydoun 2015; Prospective (4.6 y) (55)	US (Healthy Aging in Neighborhoods of Diversity across the Life Span [HANDLS] study)	24-h recall	CES-D (depression ≥ 16)	General population; n=3720; age 30–64 y	Age, sex, race, poverty status, and educational level.	n-3 PUFA (linear), men: beta= −0.00 (SE 0.17), P=0.99; women: beta= −0.07 (SE 0.17), P=0.67 n-3: n-6 PUFA ratio (linear), men: beta= −0.11 (SE 0.73), P=0.88; women: beta= −3.40 (SE 1.24), P=0.006	High

ALA, alpha linolenic acid ; BDI-Y, Beck Depression Inventory for Youth; BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression; CI, confidence intervals; CIDI-SF, Composite International Diagnostic Interview-Short Form; DASS-21, Depression, Anxiety and Stress Scales; DHA, docosahexaenoic acid; GDS, Geriatric Depression Scale; EPA, eicosapentaenoic acid; EPDS, Edimburgh Post-partum Depression Scale; HR, hazard ratio; M-CIDI, Munich-Composite International Diagnostic Interview; OR, odds ratio; PUFA, polyunsaturated fatty acid; RR, relative risk.

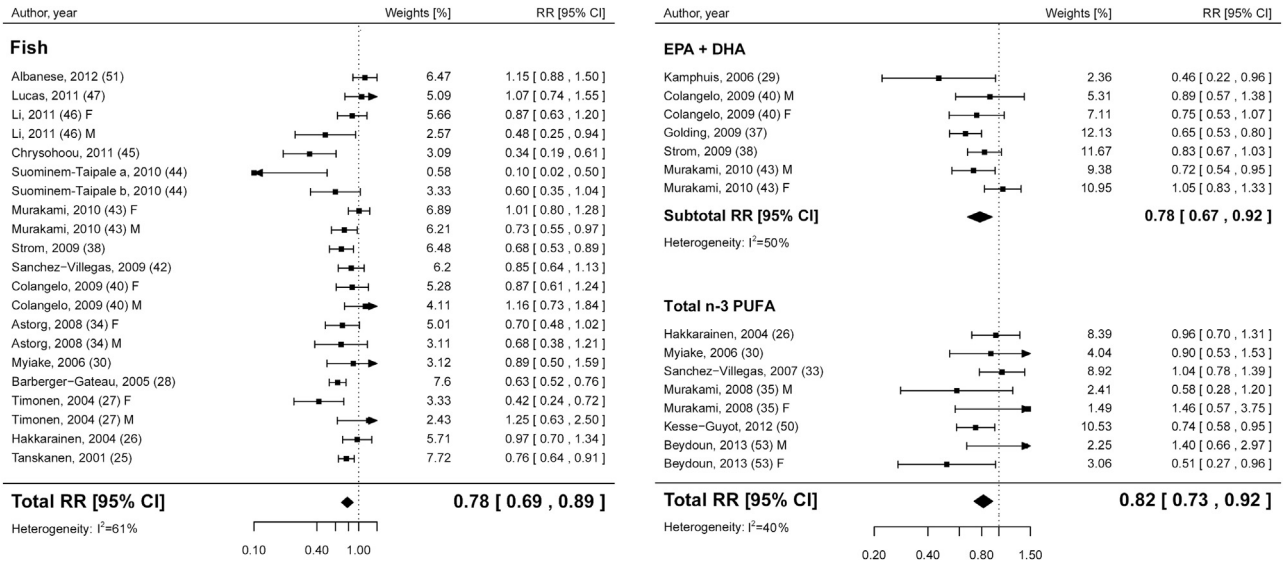

Fig. 2. Forest plot of summary relative risks (RRs) of depression for the highest versus the lowest (reference) category of fish and n-3 PUFA dietary intake.

moderate heterogeneity (I^2=61%) and little asymmetry of funnel plot (Additional Fig. 1). Exclusion of studies one at the time did not significantly changed heterogeneity or pooled risk estimate. However, the asymmetry of funnel plot depended on the dataset from the study of Suominen-Taipale et al. (2010) that accounted for small sample size and few cases of depression. Sub-group analysis provided further information on potential association between fish consumption and depression (Table 2). The most relevant association was by study location, as studies conducted in Europe scored lower RRs whereas those conducted in US or Asian countries did not reach statistical significance. Among the other sub-group analyses, pooled results from higher quality studies were not significant. Finally, regarding participants characteristics, reduced risk was found in women but not in men.

A dose-response analysis was performed including 16 studies providing the exact amount of fish for each category of exposure and resulted in a non-significant linear association between fish consumption and depression (Fig. 3). Specific doses analyses revealed that significant decreased risk was reached for 50 g/d intake (RR=0.84, 95% 0.72, 0.99; Table 3).

3.3. n-3 PUFA intake and depression

An inverse association between n-3 PUFA intake and depression was reported in 7 (Beydoun et al., 2013; Daley et al., 2014; Golding et al., 2009; Kamphuis et al., 2006; Kesse-Guyot et al., 2012; Murakami et al., 2008, 2010) out of 11 cross-sectional and 4 (Colangelo et al., 2009; Jacka et al., 2013; Lucas et al., 2011; Sanchez-Villegas et al., 2007) of 10 prospective studies. The studies by Murakami et al. (2008) and Lucas et al. (2011) reported a significant association between depression score and ALA, but not total n-3 PUFA, whereas the study of Jacka et al. (2013) reported an association with EPA intake, but not DHA. Besides the study of Lucas et al. (2011), all other articles exploring a linear association

Table 2
Subgroup analysis of risk of depression for the highest vs. lowest (reference) category of fish consumption, n-3 PUFA, and EPA+DHA intake.

Subgroup	Fish			n-3 PUFA			EPA + DHA		
	No. of datasets	RR (95% CI)	I^2	No. of datasets	RR (95% CI)	I^2	No. of datasets	RR (95% CI)	I^2
All datasets	21	0.78 (0.69, 0.89)	61%	15	0.82 (0.72, 0.94)	40%	7	0.76 (0.64, 0.90)	50%
Excluding studies on peri-natal depression	19	0.78 (0.68, 0.90)	64%	12	0.87 (0.75, 1.01)	34%	5	0.81 (0.65, 1.01)	48%
Study design									
Cross-sectional	11	0.73 (0.60, 0.89)	72%	9	0.79 (0.66, 0.95)	51%	3	0.79 (0.59, 1.06)	79%
Prospective	10	0.83 (0.70, 0.97)	42%	7	0.85 (0.73, 1.00)	19%	4	0.74 (0.61, 0.89)	0%
Study quality									
Moderate	13	0.71 (0.58, 0.86)	56%	7	0.85 (0.69, 1.04)	19%	4	0.69 (0.59, 0.81)	0%
High	8	0.86 (0.72, 1.01)	69%	8	0.82 (0.68, 0.98)	57%	3	0.82 (0.64, 1.07)	66%
Gender									
Men	5	0.81 (0.60, 1.09)	44%	5	0.76 (0.58, 0.99)	27%	3	0.73 (0.57, 0.93)	13%
Women	7	0.81 (0.67, 0.97)	56%	6	0.79 (0.64, 0.96)	55%	4	0.78 (0.62, 0.99)	69%
Study location									
Europe	11	0.66 (0.56, 0.78)	53%	6	0.87 (0.73, 1.05)	26%	3	0.66 (0.56, 0.78)	0%
Asia	3	0.88 (0.70, 1.10)	34%	5	0.87 (0.68, 1.12)	40%	2	0.87 (0.60, 1.27)	77%
US	5	0.90 (0.73, 1.12)	29%	4	0.80 (0.59, 1.09)	32%	2	0.80 (0.61, 1.05)	0%
Adjustment for dietary variables									
Yes	11	0.77 (0.62, 0.95)	67%	8	0.83 (0.69, 1.01)	50%	2	0.67 (0.57, 0.79)	0%
No	10	0.78 (0.67, 0.91)	55%	7	0.81 (0.66, 1.00)	40%	5	0.79 (0.65, 0.97)	60%
Adjustment for socio-economic variables									
Yes	19	0.79 (0.70, 0.90)	56%	14	0.80 (0.70, 0.92)	39%	7	0.76 (0.64, 0.90)	50%
No	2	0.62 (0.20, 1.90)	91%	1	1.04 (0.78, 1.39)	–	0	–	–

Abbreviations: CI, confidence intervals; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; n-3 PUFA, n-3 polyunsaturated fatty acid; RR, relative risk.

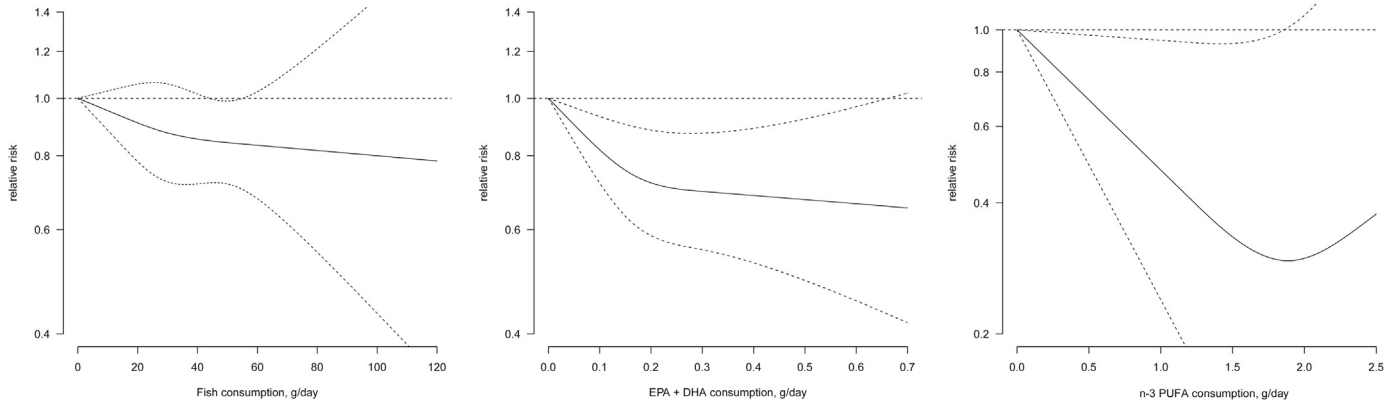

Fig. 3. Dose-response analyses of a) fish, b) n-3 PUFA, and c) EPA+DHA dietary intake and risk of depression.

between intake of n-3 PUFA and scores of depression showed no significant results. Overall, the amount of n-3 PUFA estimated across studies varied to a great extent and results of studies seem to partially reflect the categories of exposure chosen. For instance, those studies comparing the effect of extreme n-3 PUFA intakes with the highest category of exposure with particularly low [100 mg/d (Sontrop et al., 2008; Strom et al., 2009)] or high [4000 mg/d (Miyake et al., 2006; Murakami et al., 2008)] amounts reported consistently inconclusive results.

A total of 11 studies were considered for the analysis of the extreme categories of n-3 PUFA intake and depression including 15 datasets and resulted in significant reduced risk of depression (RR =0.82, 95% CI: 0.73, 0.92; Fig. 2) with moderate evidence of heterogeneity (I^2=40%) and no publication bias (Supplemental Fig. 1). When the analysis was restricted to studies exploring the association of only EPA+DHA and depression (7 datasets), the risk estimated was reduced (RR =0.78, 95% CI: 0.67, 0.92; Fig. 2). Notably, pooled risk estimates lacked of significance when studies conducted on peri-natal depression were excluded from the analysis (Table 2). Other sub-group analyses revealed similar results found for fish consumption (Table 2). Results were inconclusive for lower quality studies on n-3 PUFA and cross-sectional studies involving EPA+DHA. Grouping by geographical area led to inconclusive results when studies on n-3 PUFA were considered, whereas results were significant only in studies conducted in Europe when the main variable of interest was EPA+DHA intake (Table 2). No significant changes were found when studies were grouped by gender or type of adjustments.

The dose-response analysis demonstrated a J-shaped decreased risk of depression up to 1.8 g/d of n-3 PUFA intake (RR=0.30, 95% CI: 0.09, 0.98; Fig. 3 and Table 3). Accordingly, dose-response calculated for studies on EPA+DHA showed significant decreased risk of depression up to 0.6 g/d of EPA+ DHA intake (RR=0.66, 95% CI: 0.45, 0.97), despite non-significant decreased risk was evident also for further increment intake (Fig. 3 and Table 3).

3.4. Individual PUFAs intake and depression

Six studies (Colangelo et al., 2009; Jacka et al., 2013; Kesse-Guyot et al., 2012; Miyake et al., 2006; Murakami et al., 2008, 2010), including 9 datasets, presented risk estimates for individual intake of EPA and DHA. Pooled analysis revealed no significant decreased risk of depression for both EPA (RR=0.90, 95% CI: 0.79, 1.03) and DHA (RR=0.95, 95% CI: 0.81, 1.10; see Supplemental Fig. 2). No association was also found in pooled analysis of 4 studies exploring the association of ALA dietary intake and depression (see Supplemental Fig. 2). No insights are provided about the dose due to lack of fundamental data necessary to perform relative analysis.

Four (Beydoun et al., 2013, 2015; da Rocha and Kac, 2012; Lucas et al., 2011) out the 6 studies evaluating the possible relation between the n-3: n-6 PUFA ratio and depression reported a significant relationship. The association was tested considering the ratio increment as continuous in all the studies. Pooled analysis was performed but was lacking of crucial data (Supplemental Fig. 2).

4. Discussion

Results of this systematic review and meta-analysis supported the hypothesis that fish consumption and n-3 PUFA intake are associated with decreased risk of depression. To date, this is the first meta-analysis pooling together all relevant observational studies assessing the relation between fish, n-3 PUFA intake and depression, providing insights on dose-response relationship. A significant decreased risk was found for 50 g/d intake of fish, 1.8 g/d intake of n-3 PUFA, and 0.6 g/d intake of EPA+DHA, despite non-significant decreased risk was observed for higher intake of both fish and EPA+DHA. Large 95% CI for higher intakes may be due to objective artifacts relative to risk estimates from studies conducted in

Table 3
Dose-response analyses for various category of exposure and risk of depression.

	Dose					
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Fish	0 g/d	25 g/d	50 g/d	75 g/d	100 g/d	125 g/d
	1.00	0.87 (0.72–1.06)	0.84 (0.72–0.99)	0.82 (0.58–1.15)	0.81 (0.49–1.34)	0.78 (0.34–1.81)
n-3 PUFA	0 g/d	0.5 g/d	1 g/d	1.5 g/d	1.8 g/d	2.0 g/d
	1.00	0.69 (0.49–0.97)	0.48 (0.24–0.95)	0.33 (0.12–0.93)	0.30 (0.09–0.98)	0.30 (0.08–1.08)
EPA+DHA	*0* g/d	0.1 g/d	0.3 g/d	0.6 g/d	0.9 g/d	1.20 g/d
	1.00	0.82 (0.72–0.93)	0.70 (0.55–0.87)	0.66 (0.45–0.97)	0.63 (0.35–1.15)	0.60 (0.26–1.38)

Abbreviations: CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; n-3 PUFA, n-3 polyunsaturated fatty acid; RR, relative risk.

geographical areas with very high intake of fish/n-3 PUFA (i.e., Japan), as suggested by the sub-group analyses. Despite moderate heterogeneity among studies was present in all analyses weakening overall conclusions, these results are in line with previous findings suggesting that dietary patterns rich in fish may exert protective effects toward depression risk (Psaltopoulou et al., 2013).

A number of methodological issues of previous studies on fish, n-3 PUFA and depression have risen from this systematic review and should be discussed to suggest new strategies for future observational studies on this topic. N-3 PUFA have been hypothesized to protect by major depression through several possible pathways, such as anti-inflammatory effects (Hibbeln and Salem, 1995), neuro-endocrine modulation (Hibbeln et al., 1998), and neuroprotective/neurotrophic mechanisms (Chang et al., 2009). Recently, a study provided mechanistic insights on how inflammatory biomarkers may act as moderators of clinical response to n-3 PUFA in patients with major depressive disorder (Rapaport et al., 2015). Moreover, it has been demonstrated that n-3 PUFA supplement exert antidepressant effects especially in patients with DSM-defined major depressive disorder rather than in individuals with only non-clinically relevant depressive symptoms (Lin et al., 2012). We further reported in a meta-analysis of randomized clinical trials that n-3 PUFA supplement exert a beneficial effect in patients affected by depression, but results were more convincing in those studies conducted on patients with an established diagnosis of major depression based on clinical evaluation, weaker in patients without a clinical diagnosis, and inconsistent in randomly recruited individuals among the general population (Grosso et al., 2014b). Overall, independently of the mechanism involved, n-3 PUFA are suggested to exert their effects on major depression, rather than being considered as mood modulating agents. In contrast, psychometric tools used in most of the observational studies included in the present systematic review cannot diagnose cases of major depression, rather may identify cases of depressive status that may be biased by cases of depressed mood, emotional or anxious distress, for which n-3 PUFA are not supposed to be equally effective. In fact, despite extensively validated, all these tools can only suggest the presence of depression when a cut-off point has been reached, whereas a clinical evaluation is needed for an established diagnosis of major depression. Furthermore, a cut-off point of the scale may indicate the presence of depression, but it does not necessarily mean that different scores accounted in the scale correspond to different clinical conditions. This issue rises in those studies attempting to demonstrate a linear dose-response association between fish or n-3 PUFA consumption and the scale used to measure the depression, which reported in most of cases negative results (Appleton et al., 2007a; Kyrozis et al., 2009; Lucas et al., 2011). Moreover, with this analytic approach authors assumed a linear dose-response effect of n-3 PUFA, which is actually not demonstrated. This may also explain why even the quantile analysis in certain studies failed to demonstrate the association between n-3 PUFA and depression, since individuals being in the highest category of exposure did not necessarily indicated that they reached an amount of n-3 PUFA adequate to be effective in preventing the onset of depressive disorders. In contrast, as mentioned above, other studies compared intakes of fish or n-3 PUFA much higher than those demonstrated to be effective in preventing depression. Findings of this meta-analysis suggested a J-shaped effect of n-3 PUFA and decreased risk of depression up to 1.8 g/d intake. In line with this result, a recent study evaluating the possible relation between markers of n-3 PUFA intake and postpartum depression revealed that a non-linear curve best described the inverse relationship between the n-3 index (defined as the content of EPA+DHA in red blood cells membranes expressed as a percent of total fatty acids) in pregnancy and maternal level of depressive symptoms three months post-partum (Markhus et al., 2013). This non-linear inverse relationship has been previously reported at ecological level by other studies (Hibbeln, 2002; Hibbeln and Salem, 1995). We can speculate that a possible reason for such non-linear shape of association may depend by intake of other nutrients that can, somehow, counteract the effects of n-3 PUFA intake. Among the main candidates, n-6 PUFA and its ratio with n-3 intake have been suggested to be determinant in influencing the risk of many of the chronic diseases of high prevalence in Western societies (Simopoulos, 2002, 2006). A cross-national ecological examination of both n-6 and n-3 PUFA reported that a threshold of n-3 PUFA consumption of 750 mg/d (0.35% of energy, based on a 2000 kcal/d diet) could be sufficient to protect 98% of the population from the risk to develop depressive disorders (Hibbeln et al., 2006). Considering such threshold, none of the epidemiological studies included in this systematic review reported similar amounts, even among individuals in higher quantiles, with the exception of those conducted in Japan (Miyake et al., 2006; Murakami et al., 2008, 2010).

It has been suggested that n-3 PUFA intakes should be made dependent on concurrent intakes of n-6 PUFA, which based on the current *per capita* background available intake of LA in the United States, reaches a healthy dietary allowance of 3.5 g/d of n-3 PUFA (Hibbeln et al., 2006). Indeed, n-6 PUFA have been associated themselves to unhealthy outcomes, such as increased suicide rates in pregnant women (Vaz et al., 2014). Furthermore, dietary n-6 PUFA lowering has been reported to significantly reduce LA and increase n-3 PUFA concentrations in plasma, without altering plasma AA concentration (Taha et al., 2014). Considering the extent of influence of n-6 on n-3 PUFA intake to detect a protective effect on the most of population, this may explain the substantial inconsistency among the studies conducted in US included in this systematic review. This hypothesis is supported by the fact that four studies (Beydoun et al., 2013, 2015; da Rocha and Kac, 2012; Lucas et al., 2011) examining both n-6 and n-3 PUFAs reported a significant protective effect of decreased n-6: n-3 ratio (or increased n-3: n6 PUFA ratio), even when depression was not associated with n-3 PUFA consumption alone. Moreover, the study of Lucas et al. (2011) pointed out the attention also on the ALA: LA ratio, reporting an inverse association between depression, higher intakes of ALA and low of LA. However, the pooled analysis for n-3: n-6 PUFA ratio led to inconclusive results due to non-significant results of two studies (Kesse-Guyot et al., 2012; Miyake et al., 2006). Possible explanations may be hypothesized. In the study of Kesse-Guyot et al. (2012) the estimated ratio seemed to be much lower than the one reported in the previous studies, as the dose in the highest category of exposure corresponded to the lowest reported by Beydoun et al. (2013) and even lower than the one reported by Lucas et al. (2011). In contrast, in the study of Miyake et al. (2006), the estimated n-3 PUFA consumption and n-3: n-6 PUFA ratio in lower quantile was much higher than that reported in the other studies. Despite the n-3: n-6 PUFA ratio itself may not be independently predictive of outcome, its evaluation may result of major importance to further evaluate, perhaps adjust findings according to a more complete estimation of dietary sources of PUFA (Harris, 2006; Marventano et al., 2015).

Among the other ancillary analyses conducted in this study, we investigate whether a difference between EPA and DHA was evidence in the summary risk estimates. Among the observational studies included, only EPA neared significant results with a non-significant decreased risk of depression. This finding is in line with previous on the administration of EPA and DHA in depressive patients, which already shown that EPA, rather than DHA, seem to exert the best therapeutic effect (Politi et al., 2013; Rizzo et al., 2012; Rondanelli et al., 2010). This may be due to DHA being especially prone to peroxidation, yielding a toxic substance and more effective anti-inflammatory action of dietary EPA compared

with DHA (Sierra et al., 2008). However, further research is needed to better identify the specific role of EPA and DHA in preventing or ameliorating depression.

In addition to the aforementioned observations, a limitation of this review depends on the methodology of the studies included. Cross-sectional studies do not allow to demonstrate a causal relationship between the factors studied because the temporal variable is lacking. As well, prospective studies may suffer by misclassification of exposure, since n-3 PUFA dietary intake was assumed to be constant over the entire follow-up periods. While randomized controlled trials benefit of accurate participants selection virtually countering potential confounding factors, observational studies conducted on general population must take into account the possibility that background characteristics have a role in the final associations between the variables of interest. In light of this observation, lack of adjustment for certain variables may be a significant limitation of some studies included in this systematic review. To overcome this issue we performed some sub-group analyses considering the adjustment for both dietary and socio-economic variables, but residual confounding may exist.

In conclusion, a comprehensive analysis of available observational studies supports the hypothesis that dietary n-3 PUFA intake, especially derived by fish, decrease the risk of depression. Heterogeneity among studies was found, weakening final conclusions. However, we suggested several explanations for such inconsistency and addressed a number of limitations regarding the methodological approaches used in some studies included in the meta-analysis that may explain such contrasting results. Further research is needed to better identify whether this relation is consistent taking into account the methodological limitations retrieved in this systematic reviews, considering the non-linear relationship between n-3 PUFA intake and the risk of depression, adjusting the methodology accordingly, and providing detailed consumption of all PUFA, including ALA, EPA, DHA, and the n-3: n-6 PUFA ratio.

Contributors

GG designed the research; GG and SC conducted research; GG and AM analyzed data; SM edited tables and images; GG wrote the paper; GG, FG, and AM provided important revision for final content. All authors reviewed and approved the study content.

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Conflict of interest

All authors declare no conflicts of interest.

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Appendix A. Supporting information

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References

Albanese, E., Lombardo, F.L., Dangour, A.D., Guerra, M., Acosta, D., Huang, Y., Jacob, K.S., Llibre Rodriguez, Jde, J., Salas, A., Schonborn, C., Sosa, A.L., Williams, J., Prince, M.J., Ferri, C.P., 2012. No association between fish intake and depression in over 15,000 older adults from seven low and middle income countries–the 10/66 study. PLoS One 7, e38879.

Appleton, K.M., Peters, T.J., Hayward, R.C., Heatherley, S.V., McNaughton, S.A., Rogers, P.J., Gunnell, D., Ness, A.R., Kessler, D., 2007a. Depressed mood and n-3 polyunsaturated fatty acid intake from fish: non-linear or confounded association? Soc. Psychiatry Psychiatr. Epidemiol. 42, 100–104.

Appleton, K.M., Woodside, J.V., Yarnell, J.W., Arveiler, D., Haas, B., Amouyel, P., Montaye, M., Ferrieres, J., Ruidavets, J.B., Ducimetiere, P., Bingham, A., Evans, A., 2007b. Depressed mood and dietary fish intake: direct relationship or indirect relationship as a result of diet and lifestyle? J. Affect. Disord. 104, 217–223.

Astorg, P., Couthouis, A., Bertrais, S., Arnault, N., Meneton, P., Guesnet, P., Alessandri, J.M., Galan, P., Hercberg, S., 2008. Association of fish and long-chain n-3 polyunsaturated fatty acid intakes with the occurrence of depressive episodes in middle-aged French men and women. Prostaglandins Leukot. Essent. Fat. Acids 78, 171–182.

Barberger-Gateau, P., Jutand, M.A., Letenneur, L., Larrieu, S., Tavernier, B., Berr, C., 2005. Correlates of regular fish consumption in French elderly community dwellers: data from the three-city study. Eur. J. Clin. Nutr. 59, 817–825.

Beydoun, M.A., Fanelli Kuczmarski, M.T., Beydoun, H.A., Hibbeln, J.R., Evans, M.K., Zonderman, A.B., 2013. Omega-3 fatty acid intakes are inversely related to elevated depressive symptoms among United States women. J. Nutr. 143, 1743–1752.

Beydoun, M.A., Fanelli Kuczmarski, M.T., Beydoun, H.A., Rostant, O.S., Evans, M.K., Zonderman, A.B., 2015. Associations of the ratios of n-3 to n-6 dietary fatty acids with longitudinal changes in depressive symptoms among US women. Am. J. Epidemiol. 181, 691–705.

Bountziouka, V., Polychronopoulos, E., Zeimbekis, A., Papavenetiou, E., Ladoukaki, E., Papairakleous, N., Gotsis, E., Metallinos, G., Lionis, C., Panagiotakos, D., 2009. Long-term fish intake is associated with less severe depressive symptoms among elderly men and women: the MEDIS (MEDiterranean ISlands Elderly) epidemiological study. J. Aging Health 21, 864–880.

Bourre, J.M., 2004. Roles of unsaturated fatty acids (especially omega-3 fatty acids) in the brain at various ages and during ageing. J. Nutr. Health Aging 8, 163–174.

Bourre, J.M., 2007. Dietary omega-3 fatty acids for women. Biomed. Pharm. 61, 105–112.

Caraci, F., Copani, A., Nicoletti, F., Drago, F., 2010. Depression and Alzheimer's disease: neurobiological links and common pharmacological targets. Eur. J. Pharmacol. 626, 64–71.

Chang, C.Y., Ke, D.S., Chen, J.Y., 2009. Essential fatty acids and human brain. Acta Neurol. Taiwan 18, 231–241.

Chrysohoou, C., Tsitsinakis, G., Siassos, G., Psaltopoulou, T., Galiatsatos, N., Metaxa, V., Lazaros, G., Miliou, A., Giakoumi, E., Mylonakis, C., Zaromytidou, M., Economou, E., Triantafyllou, G., Pitsavos, C., Stefanadis, C., 2011. Fish consumption moderates depressive symptomatology in elderly men and women from the IKARIA study. Cardiol. Res. Pract. 2011, 219578.

Colangelo, L.A., He, K., Whooley, M.A., Daviglus, M.L., Liu, K., 2009. Higher dietary intake of long-chain omega-3 polyunsaturated fatty acids is inversely associated with depressive symptoms in women. Nutrition 25, 1011–1019.

da Rocha, C.M., Kac, G., 2012. High dietary ratio of omega-6 to omega-3 polyunsaturated acids during pregnancy and prevalence of post-partum depression. Matern. Child Nutr. 8, 36–48.

Daley, C., Patterson, A., Sibbritt, D., Macdonald-Wicks, L., 2014. Unsaturated fat intakes and mental health outcomes in young women from the Australian longitudinal study on women's heath. Public Health Nutr., 1–8.

De Vriese, S.R., Christophe, A.B., Maes, M., 2003. Lowered serum n-3 polyunsaturated fatty acid (PUFA) levels predict the occurrence of postpartum depression: further evidence that lowered n-PUFAs are related to major depression. Life Sci. 73, 3181–3187.

Edwards, R., Peet, M., Shay, J., Horrobin, D., 1998. Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients. J. Affect. Disord. 48, 149–155.

Gil, A., 2002. Polyunsaturated fatty acids and inflammatory diseases. Biomed. Pharm. 56, 388–396.

Giles, G.E., Mahoney, C.R., Kanarek, R.B., 2013. Omega-3 fatty acids influence mood in healthy and depressed individuals. Nutr. Rev. 71, 727–741.

Golding, J., Steer, C., Emmett, P., Davis, J.M., Hibbeln, J.R., 2009. High levels of depressive symptoms in pregnancy with low omega-3 fatty acid intake from fish. Epidemiology 20, 598–603.

Greenland, S., 1987. Quantitative methods in the review of epidemiologic literature. Epidemiol. Rev. 9, 1–30.

Grosso, G., Galvano, F., Marventano, S., Malaguarnera, M., Bucolo, C., Drago, F., Caraci, F., 2014a. Omega-3 fatty acids and depression: scientific evidence and biological mechanisms. Oxid. Med. Cell. Longev. 2014, 313570.

Grosso, G., Pajak, A., Marventano, S., Castellano, S., Galvano, F., Bucolo, C., Drago, F., Caraci, F., 2014b. Role of omega-3 fatty acids in the treatment of depressive disorders: a comprehensive meta-analysis of randomized clinical trials. PLoS One 9, e96905.

Hakkarainen, R., Partonen, T., Haukka, J., Virtamo, J., Albanes, D., Lonnqvist, J., 2004. Is low dietary intake of omega-3 fatty acids associated with depression? Am. J. Psychiatry 161, 567–569.

Hamling, J., Lee, P., Weitkunat, R., Ambuhl, M., 2008. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. Stat. Med. 27, 954–970.
Harris, W.S., 2006. The omega-6/omega-3 ratio and cardiovascular disease risk: uses and abuses. Curr. Atheroscler. Rep. 8, 453–459.
Hepgul, N., Mondelli, V., Pariante, C.M., 2010. Psychological and biological mechanisms of cytokine induced depression. Epidemiol. Psichiatr Soc. 19, 98–102.
Hibbeln, J.R., 1998. Fish consumption and major depression. Lancet 351, 1213.
Hibbeln, J.R., 2002. Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression: a cross-national, ecological analysis. J. Affect. Disord. 69, 15–29.
Hibbeln, J.R., Linnoila, M., Umhau, J.C., Rawlings, R., George, D.T., Salem Jr., N., 1998. Essential fatty acids predict metabolites of serotonin and dopamine in cerebrospinal fluid among healthy control subjects, and early- and late-onset alcoholics. Biol. Psychiatry 44, 235–242.
Hibbeln, J.R., Nieminen, L.R., Blasbalg, T.L., Riggs, J.A., Lands, W.E., 2006. Healthy intakes of n-3 and n-6 fatty acids: estimations considering worldwide diversity. Am. J. Clin. Nutr. 83, 1483S–1493S.
Hibbeln, J.R., Salem Jr., N., 1995. Dietary polyunsaturated fatty acids and depression: when cholesterol does not satisfy. Am. J. Clin. Nutr. 62, 1–9.
Huffman, J.C., Celano, C.M., Beach, S.R., Motiwala, S.R., Januzzi, J.L., 2013. Depression and cardiac disease: epidemiology, mechanisms, and diagnosis. Cardiovasc. Psychiatry Neurol. 2013, 695925.
Jacka, F.N., Pasco, J.A., Williams, L.J., Meyer, B.J., Digger, R., Berk, M., 2013. Dietary intake of fish and PUFA, and clinical depressive and anxiety disorders in women. Br. J. Nutr. 109, 2059–2066.
Kamphuis, M.H., Geerlings, M.I., Tijhuis, M.A., Kalmijn, S., Grobbee, D.E., Kromhout, D., 2006. Depression and cardiovascular mortality: a role for n-3 fatty acids? Am. J. Clin. Nutr. 84, 1513–1517.
Kesse-Guyot, E., Touvier, M., Andreeva, V.A., Jeandel, C., Ferry, M., Hercberg, S., Galan, P., 2012. Cross-sectional but not longitudinal association between n-3 fatty acid intake and depressive symptoms: results from the SU.VI.MAX 2 study. Am. J. Epidemiol. 175, 979–987.
Kyrozis, A., Psaltopoulou, T., Stathopoulos, P., Trichopoulos, D., Vassilopoulos, D., Trichopoulou, A., 2009. Dietary lipids and geriatric depression scale score among elders: the EPIC-Greece cohort. J. Psychiatr. Res. 43, 763–769.
Li, Y., Dai, Q., Ekperi, L.I., Dehal, A., Zhang, J., 2011. Fish consumption and severely depressed mood, findings from the first national nutrition follow-up study. Psychiatry Res. 190, 103–109.
Lin, P.Y., Mischoulon, D., Freeman, M.P., Matsuoka, Y., Hibbeln, J., Belmaker, R.H., Su, K.P., 2012. Are omega-3 fatty acids antidepressants or just mood-improving agents? The effect depends upon diagnosis, supplement preparation, and severity of depression. Mol. Psychiatry 17, 1161–1163, author reply 1163–1167.
Lucas, M., Mirzaei, F., O'Reilly, E.J., Pan, A., Willett, W.C., Kawachi, I., Koenen, K., Ascherio, A., 2011. Dietary intake of n-3 and n-6 fatty acids and the risk of clinical depression in women: a 10-y prospective follow-up study. Am. J. Clin. Nutr. 93, 1337–1343.
Maes, M., Yirmyia, R., Noraberg, J., Brene, S., Hibbeln, J., Perini, G., Kubera, M., Bob, P., Lerer, B., Maj, M., 2009. The inflammatory & neurodegenerative (I&ND) hypothesis of depression: leads for future research and new drug developments in depression. Metab. Brain Dis. 24, 27–53.
Markhus, M.W., Skotheim, S., Graff, I.E., Froyland, L., Braarud, H.C., Stormark, K.M., Malde, M.K., 2013. Low omega-3 index in pregnancy is a possible biological risk factor for postpartum depression. PLoS One 8, e67617.
Marventano, S., Kolacz, P., Castellano, S., Galvano, F., Buscemi, S., Mistretta, A., Grosso, G., 2015. A review of recent evidence in human studies of n-3 and n-6 PUFA intake on cardiovascular disease, cancer, and depressive disorders: does the ratio really matter? Int. J. Food Sci. Nutr. 66, 611–622.
Miyake, Y., Sasaki, S., Yokoyama, T., Tanaka, K., Ohya, Y., Fukushima, W., Saito, K., Ohfuji, S., Kiyohara, C., Hirota, Y., 2006. Risk of postpartum depression in relation to dietary fish and fat intake in Japan: the Osaka Maternal and Child Health Study. Psychol. Med. 36, 1727–1735.
Murakami, K., Miyake, Y., Sasaki, S., Tanaka, K., Arakawa, M., 2010. Fish and n-3 polyunsaturated fatty acid intake and depressive symptoms: Ryukyus child health study. Pediatrics 126, e623–e630.
Murakami, K., Mizoue, T., Sasaki, S., Ohta, M., Sato, M., Matsushita, Y., Mishima, N., 2008. Dietary intake of folate, other B vitamins, and omega-3 polyunsaturated fatty acids in relation to depressive symptoms in Japanese adults. Nutrition 24, 140–147.
Noaghiul, S., Hibbeln, J.R., 2003. Cross-national comparisons of seafood consumption and rates of bipolar disorders. Am. J. Psychiatry 160, 2222–2227.
Oddy, W.H., Hickling, S., Smith, M.A., O'Sullivan, T.A., Robinson, M., de Klerk, N.H., Beilin, L.J., Mori, T.A., Syrette, J., Zubrick, S.R., Silburn, S.R., 2011. Dietary intake of omega-3 fatty acids and risk of depressive symptoms in adolescents. Depression Anxiety 28, 582–588.
Orsini, N., Li, R., Wolk, A., Khudyakov, P., Spiegelman, D., 2012. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am. J. Epidemiol. 175, 66–73.
Parletta, N., Milte, C.M., Meyer, B.J., 2013. Nutritional modulation of cognitive function and mental health. J. Nutr. Biochem. 24, 725–743.
Patrick, R.P., Ames, B.N., 2015. Vitamin D and the omega-3 fatty acids control serotonin synthesis and action, part 2: relevance for ADHD, bipolar disorder, schizophrenia, and impulsive behavior. FASEB J. 29, 2207–2222.
Peet, M., Murphy, B., Shay, J., Horrobin, D., 1998. Depletion of omega-3 fatty acid levels in red blood cell membranes of depressive patients. Biol. Psychiatry 43, 315–319.
Politi, P., Rocchetti, M., Emanuele, E., Rondanelli, M., Barale, F., 2013. Randomized placebo-controlled trials of omega-3 polyunsaturated fatty acids in psychiatric disorders: a review of the current literature. Curr. Drug Discov. Technol. 10, 245–253.
Psaltopoulou, T., Sergentanis, T.N., Panagiotakos, D.B., Sergentanis, I.N., Kosti, R., Scarmeas, N., 2013. Mediterranean diet, stroke, cognitive impairment, and depression: a meta-analysis. Ann. Neurol. 74, 580–591.
Rapaport, M.H., Nierenberg, A.A., Schettler, P.J., Kinkead, B., Cardoos, A., Walker, R., Mischoulon, D., 2015. Inflammation as a predictive biomarker for response to omega-3 fatty acids in major depressive disorder: a proof-of-concept study. Mol. Psychiatry.
Rizzo, A.M., Corsetto, P.A., Montorfano, G., Opizzi, A., Faliva, M., Giacosa, A., Ricevuti, G., Pelucchi, C., Berra, B., Rondanelli, M., 2012. Comparison between the AA/EPA ratio in depressed and non depressed elderly females: omega-3 fatty acid supplementation correlates with improved symptoms but does not change immunological parameters. Nutr. J. 11, 82.
Rondanelli, M., Giacosa, A., Opizzi, A., Pelucchi, C., La Vecchia, C., Montorfano, G., Negroni, M., Berra, B., Politi, P., Rizzo, A.M., 2010. Effect of omega-3 fatty acids supplementation on depressive symptoms and on health-related quality of life in the treatment of elderly women with depression: a double-blind, placebo-controlled, randomized clinical trial. J. Am Coll. Nutr. 29, 55–64.
Sanchez-Villegas, A., Delgado-Rodriguez, M., Alonso, A., Schlatter, J., Lahortiga, F., Serra Majem, L., Martinez-Gonzalez, M.A., 2009. Association of the Mediterranean dietary pattern with the incidence of depression: the Seguimiento Universidad de Navarra/University of Navarra follow-up (SUN) cohort. Arch. Gen. Psychiatry 66, 1090–1098.
Sanchez-Villegas, A., Henriquez, P., Figueiras, A., Ortuno, F., Lahortiga, F., Martinez-Gonzalez, M.A., 2007. Long chain omega-3 fatty acids intake, fish consumption and mental disorders in the SUN cohort study. Eur. J. Nutr. 46, 337–346.
Sanchez-Villegas, A., Martinez-Gonzalez, M.A., 2013. Diet, a new target to prevent depression? BMC Med. 11, 3.
Sierra, S., Lara-Villoslada, F., Comalada, M., Olivares, M., Xaus, J., 2008. Dietary eicosapentaenoic acid and docosahexaenoic acid equally incorporate as decosahexaenoic acid but differ in inflammatory effects. Nutrition 24, 245–254.
Simopoulos, A.P., 2002. The importance of the ratio of omega-6/omega-3 essential fatty acids. Biomed. Pharm. 56, 365–379.
Simopoulos, A.P., 2006. Evolutionary aspects of diet, the omega-6/omega-3 ratio and genetic variation: nutritional implications for chronic diseases. Biomed. Pharm. 60, 502–507.
Sontrop, J., Avison, W.R., Evers, S.E., Speechley, K.N., Campbell, M.K., 2008. Depressive symptoms during pregnancy in relation to fish consumption and intake of n-3 polyunsaturated fatty acids. Paediatr. Perinat. Epidemiol. 22, 389–399.
Strom, M., Mortensen, E.L., Halldorsson, T.I., Thorsdottir, I., Olsen, S.F., 2009. Fish and long-chain n-3 polyunsaturated fatty acid intakes during pregnancy and risk of postpartum depression: a prospective study based on a large national birth cohort. Am. J. Clin. Nutr. 90, 149–155.
Suominen-Taipale, A.L., Partonen, T., Turunen, A.W., Mannisto, S., Jula, A., Verkasalo, P.K., 2010. Fish consumption and omega-3 polyunsaturated fatty acids in relation to depressive episodes: a cross-sectional analysis. PLoS One 5, e10530.
Taha, A.Y., Cheon, Y., Faurot, K.F., Macintosh, B., Majchrzak-Hong, S.F., Mann, J.D., Hibbeln, J.R., Ringel, A., Ramsden, C.E., 2014. Dietary omega-6 fatty acid lowering increases bioavailability of omega-3 polyunsaturated fatty acids in human plasma lipid pools. Prostaglandins Leukot. Essent. Fat. Acids 90, 151–157.
Tanskanen, A., Hibbeln, J.R., Tuomilehto, J., Uutela, A., Haukkala, A., Viinamaki, H., Lehtonen, J., Vartiainen, E., 2001. Fish consumption and depressive symptoms in the general population in Finland. Psychiatr. Serv. 52, 529–531.
Tapiero, H., Ba, G.N., Couvreur, P., Tew, K.D., 2002. Polyunsaturated fatty acids (PUFA) and eicosanoids in human health and pathologies. Biomed. Pharm. 56, 215–222.
Timonen, M., Horrobin, D., Jokelainen, J., Laitinen, J., Herva, A., Rasanen, P., 2004. Fish consumption and depression: the Northern Finland 1966 birth cohort study. J. Affect. Disord. 82, 447–452.
Vaz, J.S., Kac, G., Nardi, A.E., Hibbeln, J.R., 2014. Omega-6 fatty acids and greater likelihood of suicide risk and major depression in early pregnancy. J. Affect. Disord. 152–154, 76–82.
Wells, G.A., O'Connell, S.B., Peterson, D., Welch, J., Losos, V., Tugwell P, M., 1999. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Health Research Institute, Ottawa (Canada).