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Research paper

Naturally absorbed polyunsaturated fatty acids, lithium, and suicide-related behaviors: A case-controlled study

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ABSTRACT

Objective: Previous studies have investigated the effects of omega-3, omega-6 and lithium on suicide-related behaviors separately. This study was performed to comprehensively investigate the effects of naturally absorbed EPA, DHA, arachidonic acid and lithium in relation to suicide attempt and deliberate self-harm, with adjustment for each other.

Methods: We analyzed plasma EPA, DHA, arachidonic acid levels and serum lithium levels of 197 patients including 33 patients with suicide attempts, 18 patients with deliberate self-harm, and 146 control patients.

Results: Multivariate logistic regression analysis with adjustment for age, gender, EPA, DHA, arachidonic acid and log-transformed lithium levels revealed that the negative associations with EPA levels (adjusted OR 0.972, 95% CI 0.947–0.997, $p = 0.031$) and log-transformed lithium levels (adjusted OR 0.156, 95% CI 0.038–0.644, $p = 0.01$) and the positive association with DHA levels (adjusted OR 1.026, 95% CI 1.010–1.043, $p = 0.002$) were significant in patients with suicide attempts than in control patients. The analysis also demonstrated that the positive association with arachidonic acid levels (adjusted OR 1.015, 95% CI 1.005–1.025, $p = 0.004$) was significant in patients with deliberate self-harm than in control patients.

Limitations: The limitations are relatively small number of patients and the effects of demographics of individual patients could not be adjusted for the analyses.

Conclusions: The present findings suggest that, as naturally absorbed nutrients, higher EPA and lithium levels may be associated with less suicide attempt, and that higher arachidonic acid levels may be associated with more deliberate self-harm.

1. Introduction

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (omega-3 fatty acids) have been reported to be effective for depression (Grosso et al., 2016; Sarris et al., 2016; Hallahan et al., 2016; Bloch and Hannestad, 2012; Lin et al., 2010), with studies favoring EPA rather than DHA as more effective (Sarris et al., 2016; Hallahan et al., 2016; Martins, 2009). However, the effects of omega-3 fatty acids on suicide appear to be inconclusive (Pompili et al., 2017) because large epidemiological studies (Poudel-Tandukar et al., 2011; Tsai et al., 2014) have shown no supportive evidence for the association between lower suicide risk and a high intake of fish, EPA and DHA. On the other hand, arachidonic acid, one of the omega-6 fatty acids, is reportedly higher among women with greater suicide risk (Vaz et al., 2014), whereas bipolar patients who have attempted suicide have shown lower levels of arachidonic acid when compared to those who did not attempt suicide (Evans et al., 2012). Clearly, these findings are conflicting.

In another line of evidence regarding lithium effects on suicide in mood disorders (Smith and Cipriani, 2017; Song et al., 2017; Terao et al., 2018) naturally occurring lithium can be an important factor in preventing suicide behavior. Trace lithium has been reported to be associated with low suicide rates in one observational study

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(Kanehisa et al., 2017) and in several epidemiological studies (Schrauzer and Shrestha, 1990; Ohgami et al., 2009; Kapsuta et al., 2011; Ishii et al., 2015; Shiotsuki et al., 2016; Ishii and Terao, 2018), although uptake of lithium from environmental ingestion (e.g., trace levels in tap water) as measured in serum lithium levels (median 0.00,072 mEq/L)(Kanehisa et al., 2017) is much lower than the level recommended for therapeutic use (approximately 0.4 to 1.0 mEq/L). On the other hand, lithium levels in tap water had a negative association with depressive symptoms and interpersonal violence but not with suicidal behaviors amongst the general population of adolescents (Ando et al., 2017), indicating that the effect of trace lithium on suicide is not fully established.

It has been suggested that elevated immune-inflammatory signaling may contribute to mood dysregulation by reducing frontal-limbic white and gray matter structural and functional integrity and/or altering serotonin neurotransmission, and that medications such as lithium that are efficacious in the treatment of mood disorders downregulate immune-inflammatory signaling while adjunctive treatment with anti-inflammatory agents, including long-chain omega-3 fatty acids, augment treatment response (McNamara and Lotrich, 2012). However, it should be noted that previous studies have investigated the effects of omega-3, omega-6 and lithium on suicide-related behaviors separately. In addition, most have focused on patients receiving lithium therapy or omega fatty acids supplementation, but not on patients without lithium therapy or omega fatty acids supplementation (i.e., naturally absorbed ones as nutrients).

As such, the present study aimed to comprehensively investigate the effects of naturally absorbed EPA, DHA, arachidonic acid, and trace lithium on suicide attempts and deliberate self-harm with adjustment for each other.

2. Methods

2.1. Study design and participants

The sample of the present study overlapped with that of our previous study (Kanehisa et al., 2017) where we investigated the effect of only lithium on suicide-related behaviors, showing that patients with suicide attempts had significantly lower lithium levels than control patients. The present study collected more patients during the prolonged observational period, extended the purpose of the study to investigating the effects of not only lithium but also EPA, DHA, and arachidonic acid on suicide-related behaviors with adjustment for each other. This study excluded patients younger than 20 years old, deceased patients, patients with schizophrenia, and undergoing lithium therapy or patients taking omega-3 fatty acids.

In detail, between Apr 1, 2013 and Sep 30, 2017, 5030 consecutive patients were ascertained at a university emergency department. They suffered from injury, intoxication, or acute exacerbation of internal disease. For this study, 3033 patients with acute exacerbation of internal disease were excluded because they were not associated from suicide attempt or deliberate self-harm. As shown in Fig. 1, 1997 patients suffering from intoxication or injury were included because intoxication and injury may be at least partially derived from suicide attempt and deliberate self-harm. Patients younger than 20 years were excluded as in Japan people aged 20 or more are regarded as adults who are able to provide informed consent by themselves. Patients suffering from schizophrenia were also excluded because it is difficult to determine whether their suicide attempts were induced by the intent to end their life or by psychotic symptoms such as auditory hallucinations.

Of the 1997 patients, there were 197 patients who gave informed consent with the measurement of serum lithium levels and plasma EPA, DHA and arachidonic acid levels. Among them, 51 patients suffered from deliberate self-harm or suicide attempts according to Silverman et al. (2007) revised nomenclature for the study of suicide and suicidal behaviors, whereby their use of the term *suicide attempt* relates specifically to a self-inflicted act with the intent to end one's life and is distinguished from self-harm and undetermined suicide-related behavior. Finally, as shown in Fig. 1, there were 197 patients consisting of 18 patients with deliberate self-harm, 33 patients with suicide attempts, and 146 control patients. Table 1 shows the type of injury or intoxication and their respective mental disorders which were diagnosed by clinical psychiatrists according to DSM-IV-TR within 2 days after admission. Most of the patients suffering from mental disorder took regular prescribed medication. This study was approved by the ethical committee of Oita University, Faculty of Medicine and all patients gave written informed consent.

2.2. Procedures

At the university emergency department, routine blood sampling was performed at the initial visit. After individual patients recovered, written informed consent was taken and, if they agreed, we used a remnant of the blood to measure plasma EPA, DHA, arachidonic acid and serum lithium levels. Plasma EPA, DHA and arachidonic acid levels were measured by a third party (Special Reference Laboratories) using gas-chromatography, where the minimum amounts of EPA, DHA and arachidonic acid which can be measured were 0.2, 0.3, and 0.2 µg/mL, respectively. Serum lithium levels were also previously measured by a third party (Oita Pharmaceutical Association Laboratory Centre) using mass spectrometry, where the minimum amount of lithium which can be measured was 1 µg/L until Dec 31, 2016. Alternatively and thereafter, serum lithium levels were measured by two of the authors (T.M. and K.Y.) who were blind to the data of the patients using mass spectrometry, where the minimum amount of lithium which can be measured was 0.15 µg/L. The distribution of lithium levels was considerably skewed and we thus employed log-transformation in order to use parametric statistical procedures; however, the distributions of EPA, DHA and arachidonic acid were neither deviated nor log-transformed.

2.3. Statistical analyses

The patient's characteristics and their EPA, DHA, arachidonic acid and log-transformed lithium levels were compared between the suicide attempts group, the deliberate self-harm group and the control group in a one-way ANOVA with post-hoc Bonferroni test for continuous variables, and with χ^2 test for categorical variables. Also, the association of gender and age with EPA, DHA, arachidonic acid and log-transformed lithium levels were examined with unpaired *t*-test and Pearson's correlation coefficient. Moreover, multivariate logistic regression analyses using the Wald test were performed to determine whether suicide attempts and deliberate self-harm were predicted by age, gender, EPA, DHA, arachidonic acid and log-transformed lithium in comparison to control group as a reference. Data was analyzed with SPSS version 24 for Windows.

3. Results

The patients comprised 123 males and 74 females and the mean age was 52.2 years (SD = 20.1, range = 20–89). The mean serum lithium level was 5.9 µg/L (SD = 4.0, range = 0.65–23.0) and the mean log-transformed lithium level was 0.68 (SD = 0.29, range = −0.19–1.36). The mean of EPA, DHA and arachidonic acid was 45.5 µg/mL (SD = 29.5, range = 6.1–172.4), 108.3 µg/mL (SD = 43.3, range = 35.9–270.1), 180.9 µg/mL (SD = 53.7, range = 77.0–387.3), respectively. Gender was not significantly associated with EPA, DHA, arachidonic acid or log-transformed lithium levels whereas age was significantly and positively associated with EPA and DHA, but not with arachidonic acid or log-transformed lithium levels.

As shown in Table 1, patients with suicide attempts and control patients included significantly more male patients or less female

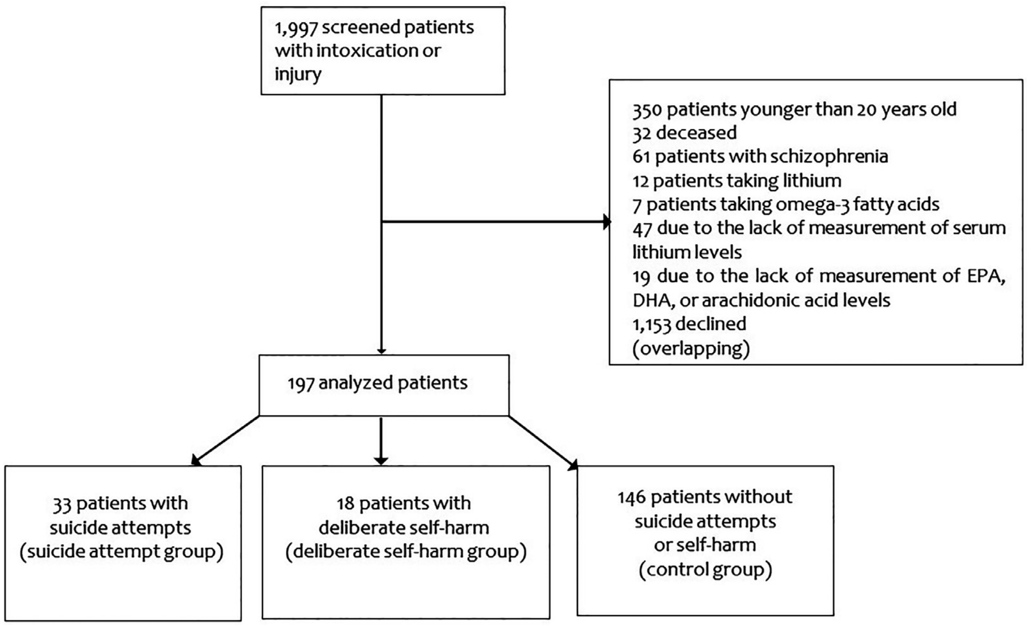

Fig. 1. Study flow chart. This figure shows how the patients were collected and entered in the present study.

Table 1
The characteristics, type of injury or intoxication, and mental disorders of suicide attempts group, deliberate self-harm group, and control groups.

	Suicide attempts (n = 33)	Deliberate self-harm (n = 18)	Control (N = 146)	Statistics
Male: Female	21:12	6:12	96:50	$x^2 = 7.2$, $p = 0.027$
Age	48.8 (19.1, 42.1–55.6)	45.2 (17.3, 36.6–53.8)	53.9 (50.5–57.2)	$F = 2.1$, $p = 0.13$
Type of injury or intoxication				
Traffic accident	1	0	74	
Falls	1	4	41	
Crushed accident	0	0	17	$x^2 = 156.5$, $p < 0.0001$
Cut wound or Stab wound	7	3	6	
Heat burn	0	0	5	
Struck accidentally	0	0	3	
Hanging	3	1	0	
Intoxication	21	10	0	
Mental disorders				
Depression	13	6	3	
Adjustment disorder	8	0	0	
Bipolar disorder	5	2	0	
Anxiety disorder	2	2	2	
Major neurocognitive disorder	2	1	3	$x^2 = 208.0$, $p < 0.0001$
Borderline personality disorder	0	3	0	
Alcohol use disorder	0	1	1	
Stimulant use disorder	1	0	0	
Intellectual disability	0	1	0	
Autism spectrum disorder	0	1	0	
Insomnia	1	1	1	
Sequela from head trauma	1	0	0	
Unspecified	0	0	2	
None	0	0	134	

patients than patients with deliberate self-harm. The type of injury or intoxication was significantly different, where patients with suicide attempts and patients with deliberate self-harm showed more incidences of intoxication, whereas control patients met with more traffic accidents, falls, or crushed accidents. Also, patients with suicide attempts and patients with deliberate self-harm had significantly more mental disorders than control patients.

As shown in Table 2, ANOVA testing revealed significant differences in arachidonic acid and log-transformed lithium levels between the three groups. In arachidonic acid levels, post-hoc Bonferroni test showed that patients with deliberate self-harm had significantly higher arachidonic acid levels than control patients. Also, in log-transformed lithium levels, post-hoc Bonferroni test showed that patients with suicide attempts had significantly lower log-transformed lithium levels than control patients.

As shown in Table 3, multivariate logistic regression analysis with adjustment for age, gender, EPA, DHA, arachidonic acid and log-transformed lithium revealed that the positive association with DHA and the negative associations with EPA and log-transformed lithium levels were significant in patients with suicide attempts than in control patients, and that the positive association with arachidonic acid levels was significant in patients with deliberate self-harm than in control patients.

Table 2
EPA, DHA, Arachidonic acid, and log-transformed lithium levels of suicide attempts group, deliberate self-harm group, and control group.

	Suicide attempts (*n* = 33)	Deliberate self-harm (*n* = 18)	Control (*n* = 146)	Statistics
EPA (μg/mL)	42.2 (27.3, 32.5–51.9)	36.4 (29.7, 21.6–51.2)	47.3 (29.8, 42.5–52.2)	$F = 1.36$, $p = 0.26$
DHA (μg/mL)	115.2 (47.5, 98.4–132.1)	102.7 (52.5, 76.6–128.8)	107.5 (41.2, 100.7–114.2)	$F = 0.60$, $p = 0.56$
Arachidonic acid (μg/mL)	181.4 (62.4, 159.3–203.6)	213.6 (53.9, 186.8–240.4)	176.7 (50.5, 168.5–185.0)	$F = 3.88$, $p = 0.022$
Log-transformed lithium levels	0.56 (0.32, 0.45–0.67)	0.75 (0.24, 0.63–0.87)	0.70 (0.28, 0.65–0.75)	$F = 3.82$, $p = 0.024$
Mean (SD, 95%CI)				

ANOVA revealed significant differences in arachidonic acid and log-transformed lithium levels between the three groups. In arachidonic acid levels, post-hoc Bonferroni test showed that patients with deliberate self-harm had significantly higher arachidonic acid levels than patients with control patients. Also, in log-transformed lithium levels, post-hoc Bonferroni test showed that patients with suicide attempts had significantly lower log-transformed lithium levels than control patients.

Table 3
Multivariate logistic regression analyses of the suicide attempts group and deliberate self-harm group with control group as a reference.

	Odds ratio (95% CI)	*p* value
Suicide attempts group (*n* = 33)		
Intercept		0.710
Gender (female = 0, male = 1)	1.180 (0.505–2.759)	0.702
Age	0.977 (0.951–1.003)	0.088
Log-transformed lithium levels	0.156 (0.038–0.644)	0.010
EPA	0.972 (0.947–0.997)	0.031
DHA	1.026 (1.010–1.043)	0.002
Arachidonic acid	0.998 (0.989–1.007)	0.598
Deliberate self-harm group (*n* = 18)		
Intercept		0.004
Gender (female = 0, male = 1)	0.207 (0.065–0.657)	0.008
Age	0.997 (0.963–1.032)	0.846
Log-transformed lithium levels	3.094 (0.380–25.187)	0.291
EPA	0.965 (0.928–1.003)	0.073
DHA	1.006 (0.983–1.030)	0.590
Arachidonic acid	1.015 (1.005–1.025)	0.004
Reference: control group (*n* = 146): Mean (95% CI)		

Multivariate logistic regression analysis with adjustment for age, gender, EPA, DHA, arachidonic acid and log-transformed lithium revealed that the positive association with arachidonic acid levels was significant in patients with deliberate self-harm than in control patients, and that the positive association with DHA and the negative associations with EPA and log-transformed lithium levels were significant in patients with suicide attempts than in control patients.

4. Discussion

The main findings of the present study are that DHA levels were positively associated with suicide attempts, whereas EPA and log-transformed lithium levels were negatively associated with suicide attempts, and that arachidonic acid levels were positively associated with deliberate self-harm. The significantly negative association between lithium levels and suicide attempts after adjustment for EPA, DHA and arachidonic acid levels further support our previous findings that patients with suicide attempts had significantly lower lithium levels than control patients after adjustment for age and gender (Kanehisa et al., 2017). Hence, despite the nature of the present observational study which cannot show the causality, one possibility is that both EPA and lithium may be protective factors against suicide attempts, whereas arachidonic acid and DHA may be risk factors for deliberate self-harm and suicide attempts, respectively. It therefore follows that there may be clear differences in individual levels of naturally occurring nutrients in people who engage in suicide attempts or deliberate self-harm which raises the possibility of nutritional prevention strategies for such behavior. Presently, this suggestion is tentative given that our study was cross-sectional and, strictly speaking, such cause-effect relationship cannot be assumed. Nonetheless, to our knowledge, this is the first study to comprehensively investigate the effects of EPA, DHA, arachidonic acid and lithium on suicide and deliberate self-harm, and these findings seem to be robust and important.

Importantly, as shown in Table 3, the odds ratio of log-transformed lithium levels (0.156, 95% CI 0.038–0.644) was significantly lower than that of EPA levels (0.972, 95% CI 0.947–0.997) in comparison to control group as a reference, suggesting that log-transformed lithium may show a stronger association with lower rate of suicide attempts than EPA. On the other hand, arachidonic acid was the only factor other than gender which was significantly and positively associated with deliberate self-harm (the odds ratio 1.015, 95% CI 1.005–1.025), suggesting that arachidonic acid may be associated with more deliberate self-harm. These findings may be counter-intuitive because one would assume that the results in those with suicide attempts in terms of arachidonic acid for example would be on a continuum of severity compared to patients with self-harm. According to Silverman et al. (2007) revised nomenclature which we used in this study, *suicide attempt* relates specifically to a self-inflicted act with the intent to end one's life, and is distinguished from self-harm. Therefore, arachidonic acid may induce a self-inflict act without the intent to end one's life. Also, arachidonic acid is a substrate for the synthesis of prostacyclins, thromboxanes, and prostaglandins which stimulate the synthesis of inflammatory cytokines (Lotrich et al., 2013), and may exacerbate depression and probably induce deliberate self-harm on the extended line of inflammation hypothesis of depression (Martins, 2009).

The present study measured plasma EPA, DHA and arachidonic acid. Several previous studies measured erythrocyte EPA, DHA and arachidonic acid. The coefficients (*rs*) of EPA and DHA in plasma in correlation with brain tissue were 0.78 ($p < 0.001$) and 0.80 ($p < 0.001$) while the *rs* of EPA and DHA in erythrocyte in correlation with brain tissue were 0.78 ($p < 0.001$) and 0.80 ($p < 0.001$), respectively (Lin et al., 2010). However, arachidonic acid levels in plasma or erythrocyte might not be as apparent in the brain (Lin et al., 2010). Therefore, caution is warranted in interpreting the findings relating to plasma arachidonic acid levels.

Although both EPA and DHA belong to omega-3 fatty acids, EPA is important in balancing immune and neuronal functions by antagonizing membrane arachidonic acid and reducing prostaglandin E_2 synthesis (Lin et al., 2010). EPA has also been reported as more effective in reducing inflammation in the brain than DHA which is associated with neuronal membrane stability and the functions of serotonin and dopamine transmission (Lin et al., 2010). Also, EPA, but not DHA, can decrease the production of arachidonic acid by inhibiting delta-5-desaturase activity, compete with arachidonic acid as a substrate for phospholipase A2, and can be converted into anti-inflammatory prostaglandins and leukotrienes (Rappaport et al., 2016). This can account for the superiority of EPA to DHA in the context of inflammation hypothesis of depression (Martins, 2009). Also, in traumatized patients at risk of developing PTSD, DHA supplementation was not found to be superior to placebo (Matsuoka et al., 2015), and EPA but not DHA was associated with better QOL (Noguchi et al., 2017). The superiority of EPA to DHA was reflected in patients with suicide attempts in the present study. Although arachidonic acid and DHA may be risk factors for deliberate self-harm and suicide attempt, to our knowledge, there is no biological evidence that DHA may be a risk factor for suicide attempt. Rather, previous studies in China (Huan et al., 2004) and the

U.S. (Lewis et al., 2011) have revealed that lower peripheral DHA may be a risk factor for suicide, whereas population-based cohort studies in Japan have not supported a protective role of higher intake of fish, EPA or DHA (Poudel-Tandukar et al., 2011). Considering these findings, the results of this study indicate that high DHA levels in people attempting suicide could be the result of a compensatory process for the upstream EPA decrease. Therefore, it seems likely that high DHA levels may be an effect but not a cause of suicide attempts. At the moment, however, the interpretation of the increased DHA in suicide attempt should be put off. Further studies including intervention with fish oil should be conducted to prospectively assess whether long-term use of omega-3 including DHA may have a preventive role in attenuating suicide attempts.

It has been suggested that arachidonic acid hyper-metabolism contributes to bipolar disorder pathophysiology, and a combined high omega-3 plus low omega-6 diet was proposed (Saunders et al., 2016a, 2016b). In addition to the above mentioned proposal, the present findings imply that low arachidonic acid levels may be effective for deliberate self-harm while high EPA and high lithium levels may be effective for suicide attempts. Thus, the combination of elevating EPA and lithium levels and decreasing arachidonic acid levels may be useful not only in the case of bipolar disorder but also in various other patients with suicide attempts and/or deliberate self-harm.

With regard to the effect of lithium on suicide attempt, it has been observed that lithium administration decreases impulsive aggressive behavior, and impulsivity and aggression have been associated with death by suicide and are among the most frequently implicated risk factors for engaging in suicidal behavior (Sher, 2015). As such, higher levels of lithium in the drinking water may decrease suicide rates by reducing impulsivity and aggression.

This is the first study to comprehensively investigate the effects of EPA, DHA, arachidonic acid and lithium on suicide and deliberate self-harm. The limitations of the present study are relatively small number of patients who were nearly 10% response rate rather small and prone to selection bias. Another limitation is misassessment between suicide and deliberate self-harm. Although we asked the intent to end one's life to the patient within 1 or 2 days after they recovered, it is difficult to differentiate them. Moreover, the effects of mental disorders, psychotropics, and social background of individual patients could not be adjusted for the analyses.

In conclusion, the present findings suggest that, as naturally absorbed nutrients, higher EPA and higher lithium levels may be associated with less suicide attempt, and that higher arachidonic acid levels may be associated with more deliberate self-harm.

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The supporting foundation had no involvement in study design, the collection, analysis, or interpretation of data, writing of the report; or in the decision to submit the article for publication

Conflict of interest

Takeshi Terao has received lecture fees from Mochida, Takeda, and Taisho-Toyama, and Yutaka Matsuoka has received lecture fees from Takeda. The other authors declare no conflict of interest.

Contributors

Drs Kurosawa and Terao designed the study and wrote the protocol. Drs Kurosawa and Terao managed the literature searches and analyses. Drs Kurosawa, Kanehisa, Shiotsuki, Ishii, Takenaka, and Sakamoto collected the data. Drs Matsukawa and Yokoyama measured serum lithium levels. Drs Ando, Nishida, and Matsuoka provided useful information for this study and discussed the results. Dr Kurosawa wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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None.

References

Ando, S., Koike, S., Shimodera, S., Fujito, R., Sawada, K., Terao, T., et al., 2017. Lithium levels in tap water and the mental health problems of adolescents: an individual-level cross-sectional survey. J. Clin. Psychiatry 78, e252–e256.

Bloch, M.H., Hannestad, J., 2012. Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis. Mol. Psychiatry 17, 1272–1282.

Evans, S.J., Prossin, A.R., Harrington, G.J., Kamali, M., Ellingrod, V.L., Burant, C.F., et al., 2012. Fats and factors: lipid profiles associate with personality factors and suicidal history in bipolar subjects. PLoS One 7, e29297.

Grosso, G., Micek, A., Marventano, S., Castellano, S., Mistretta, A., Pajak, A., et al., 2016. Dietary n-3 PUFA, fish consumption and depression: a systematic review and meta-analysis of observational studies. J. Affect. Disord. 205, 269–281.

Hallahan, B., Ryan, T., Hibbeln, J.R., Murray, I.T., Glynn, S., Ramsden, C.E., et al., 2016. Efficacy of omega-3 highly unsaturated fatty acids in the treatment of depression. Br. J. Psychiatry 209, 192–201.

Huan, M., Hamazaki, K., Sun, Y., Itomura, M., Liu, H., Kang, W., et al., 2004. Suicide attempt and *n*-3 fatty acid levels in red blood cells: a case control study in China. Biol. Psychiatry 56, 490–496.

Ishii, N., Terao, T., Araki, Y., Kohno, K., Mizokami, Y., Shiotsuki, I., et al., 2015. Low male suicide and lithium in drinking water. J. Clin. Psychiatry 76, 319–326.

Ishii, N., Terao, T., 2018. Trace lithium and mental health. J. Neural Transm. (Vienna) 125, 223–227.

Kanehisa, M., Terao, T., Shiotsuki, I., Kurosawa, K., Takenaka, R., Sakamoto, T., et al., 2017. Serum lithium levels and suicide attempts: a case-controlled comparison in lithium therapy-naive individuals. Psychopharmacology (Berl) 234, 3335–3342.

Kapusta, N.D., Mossaheb, N., Etzersdorfer, E., Hlavin, G., Thau, K., Willeit, M., et al., 2011. Lithium in drinking water and suicide mortality. Br. J. Psychiatry 198, 346–350.

Lewis, M.D., Hibbeln, J.R., Johnson, J.E., Lin, Y.H., Hyun, D.Y., Loewke, J.D., 2011. Suicide deaths of active-duty US military and omega-3 fatty-acid status: a case-control comparison. J. Clin. Psychiatry 72, 1585–1590.

Lin, P.Y., Huang, S.Y., Su, K.P., 2010. A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression. Biol. Psychiatry 68, 140–147.

Lotrich, F.E., Sears, B., McNamara, R.K., 2013. Elevated ratio of arachidonic acid to long-chain omega-3 fatty acids predicts depression development following interferon-alpha treatment: relationship with interleukin-6. Brain Behav. Immun. 31, 48–53.

McNamara R.K., Lotrich F.E. 2012. Elevated immune-inflammatory signaling in mood disorders: a new therapeutic target? Expert Rev. Neurother. 12: 1143–1161.

Martins, J.G., 2009. EPA but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty acid supplementation in depression: evidence from a meta-analysis of randomized controlled trials. J. Am. Coll. Nutr. 28, 525–542.

Matsuoka, Y., Nishi, D., Hamazaki, K., Yonemoto, N., Matsumura, K., Noguchi, H., et al., 2015. Docosahexaenoic acid for selective prevention of posttraumatic stress disorder among severely injured patients: a randomized, placebo-controlled trial. J. Clin. Psychiatry 76, e1015–e1022.

Noguchi, H., Nishi, D., Matsumura, K., Hamazaki, K., Hamazaki, T., Matsuoka, Y.J., 2017. Limited effect of omega-3 fatty acids on the quality of life in survivors of traumatic injury: a randomized, placebo-controlled trial. Prostaglandins Leukot. Essent. Fatty Acids 127, 1–5.

Ohgami, H., Terao, T., Shiotsuki, I., Ishii, N., Iwata, N., 2009. Lithium levels in drinking water and risk of suicide. Br. J. Psychiatry 194, 464–465.

Pompili, M., Longo, L., Dominici, G., Serafini, G., Lamis, D.A., Sarris, J., et al., 2017. Polyunsaturated fatty acids and suicide risk in mood disorders: a systematic review. Prog. Neuropsychopharmacol. Biol. Psychiatry 74, 43–56.

Poudel-Tandukar, K., Nanri, A., Iwasaki, M., Mizoue, T., Matsushita, Y., Takahashi, Y., et al., 2011. Long chain *n*-3 fatty acids intake, fish consumption and suicide in a cohort of Japanese men and women–the Japan Public Health Center-based (JPHC) prospective study. J. Affect. Disord. 129, 282–288.

Rapaport, M.H., Nierenberg, A.A., Schettler, P.J., Kinkead, B., Cardoos, A., Walker, R., et al., 2016. Inflammation as a predictive biomarker for response to omega-3 fatty acids in major depressive disorder: a proof-of-concept study. Mol. Psychiatry 21, 71–79.

Sarris, J., Murphy, J., Mischoulon, D., Papakostas, G.I., Fava, M., Berk, M., et al., 2016. Adjunctive nutraceuticals for depression: a systematic review and meta-analyses. Am. J. Psychiatry 173, 575–587.

Saunders, E.F., Ramsden, C.E., Sherazy, M.S., Gelenberg, A.J., Davis, J.M., Rapoport, S.I., 2016a. Omega-3 and Omega-6 polyunsaturated fatty acids in bipolar disorder: a review of biomarker and treatment studies. J. Clin. Psychiatry 77, e1301–e1308.

Saunders, E.F., Ramsden, C.E., Sherazy, M.S., Gelenberg, A.J., Davis, J.M., Rapoport, S.I., 2016b. Reconsidering dietary polyunsaturated fatty acids in bipolar disorder: a translational picture. J. Clin. Psychiatry 77, e1342–e1347.
Schrauzer, G.N., Shrestha, K.P., 1990. Lithium in drinking water and the incidences of crimes, suicides, and arrests related to drug addictions. Biol. Trace Elem. Res. 25, 105–113.
Sher, L., 2015. Suicide in men. J. Clin. Psychiatry 76, e371–e372.
Shiotsuki, I., Terao, T., Ishii, N., Takeuchi, S., Kuroda, Y., Kohno, K., et al., 2016. Trace lithium is inversely associated with male suicide after adjustment of climatic factors. J. Affect. Disord. 189, 282–286.
Silverman, M.M., Berman, A.L., Sanddal, N.D., O'carroll, P.W., Joiner, T.E., 2007. Rebuilding the tower of Babel: a revised nomenclature for the study of suicide and suicidal behaviors. Part 2: Suicide-related ideations, communications, and behaviors. Suicide Life Threat. Behav. 37, 264–277.
Smith, K.A., Cipriani, A., 2017. Lithium and suicide in mood disorders: updated meta-review of the scientific literature. Bipolar Disord. 19, 575–586.
Song, J., Sjölander, A., Joas, E., Bergen, S.E., Runeson, B., Larsson, H., et al., 2017. Suicidal behavior during lithium and valproate treatment: a within-individual 8-year prospective study of 50,000 patients with bipolar disorder. Am. J. Psychiatry 174, 795–802.
Terao, T., Kanehisa, M., Shiotsuki, I., Ishii, N., 2018. Mixed features in bipolar I disorder and the effect of lithium on suicide. Am. J. Psychiatry 175, 80.
Tsai, A.C., Lucas, M., Okereke, O.I., O'Reilly, E.J., Mirzaei, F., Kawachi, I., et al., 2014. Suicide mortality in relation to dietary intake of *n*-3 and *n*-6 polyunsaturated fatty acids and fish: equivocal findings from 3 large US cohort studies. Am. J. Epidemiol. 179, 1458–1466.
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.