Depression and adipose essential polyunsaturated fatty acids

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Summary The objective of the present study was to investigate the relation between adipose tissue polyunsaturated fatty acids, an index of long-term or habitual fatty acid dietary intake, and depression. The sample consisted of 247 healthy adults (146 males, 101 females) from the island of Crete. The number of subjects with complete data on all variables studied was 139. Subjects were examined at the Preventive Medicine and Nutrition Clinic of the University of Crete. Depression was assessed through the use of the Zung Self-rating Depression Scale. Mildly depressed subjects had significantly reduced (−34.6%) adipose tissue docosahexaenoic acid (DHA) levels than non-depressed subjects. Multiple linear regression analysis indicated that depression related negatively to adipose tissue DHA levels. In line with the findings of other studies, the observed negative relation between adipose tissue DHA and depression, in the present study, appears to indicate increasing long-term dietary DHA intakes with decreasing depression. This is the first literature report of a relation between adipose tissue DHA and depression. Depression has been reported to be associated with increased cytokine production, such as IL-1, IL-2, IL-6, INF-γ and INF-α. On the other hand, fish oil and omega-3 fatty acids have been reported to inhibit cytokine synthesis. The observed negative relation between adipose DHA and depression, therefore, may stem from the inhibiting effect of DHA on cytokine synthesis.

INTRODUCTION

Depression constitutes the most common psychiatric disorder in adults and a major health problem in the elderly. It has been reported that the incidence of depression has increased, while the age of onset of depression has decreased in the 20th century. Depression is associated with increases in all-cause mortality, particularly in men. It appears that increased consumption of fish is associated with decreases in depression prevalence. The main dietary sources of docosahexaenoic acid (c22:6 n-3) (DHA), a long-chain polyunsaturated fatty acid (PUFA) of the n-3 family, are fish and mother’s milk. There are indications that depletions in DHA and other long-chain n-3 PUFAs may be associated with depression. Compared to healthy controls, depressed patients had significant depletions of red blood cell membrane phospholipid n-3 long-chain polyunsaturates, particularly DHA. In another study, significant depletions of red blood cell membrane n-3 PUFAs were observed in depressed patients as opposed to healthy controls. Furthermore, red blood cell membrane levels as well as dietary intake of n-3 polyunsaturates correlated negatively with depression severity. Another study reported a significant negative correlation between erythrocyte phospholipid eicosapentaenoic acid (c20:5 n-3) (EPA) levels and depression severity in a depressed group. However, not only n-3 polyunsaturates, but also PUFAs of the n-6 family were implicated in depression. Specifically, the ratio of n-6 polyunsaturated arachidonic acid (c20:4 n-6) (AA) to EPA as well as the ratio of total n-6/n-3 polyunsaturates in erythrocytes correlated positively to depression severity. In another study, major depressed patients had significantly elevated n-6/n-3 fatty acid ratios in cholesteryl esters and significantly elevated AA/EPA ratios in both cholesteryl esters and...
phospholipids than minor depressed patients or healthy controls. Major depressed patients had significantly decreased n-3 polyunsaturates in serum cholesteryl esters and significantly decreased EPA in cholesteryl esters and phospholipids than minor depressed patients or healthy controls. Finally, another study reported significantly increased AA/EPA ratios and significantly decreased n-3 polyunsaturates in serum cholesteryl esters and phospholipids of major depressed patients as opposed to healthy controls. However, not all studies have shown decreases in n-3 PUFAs in depressed patients as opposed to control subjects. Specifically, two studies have shown significant increases rather than decreases of erythrocyte and plasma choline phosphoglyceride EPA and DHA levels in depressed patients as opposed to healthy controls. Nevertheless, given that plasma phospholipids and cholesteryl esters are markers of fatty acid intake of the past few weeks, the decreased n-3 PUFAs in depression reported by the bulk of the studies appears to reflect, in part, a corresponding reduced consumption in the particular fatty acids. It is worth noting that none of these studies implemented adipose tissue fatty acid measures, a biomarker of long-term (1-3 year) or habitual dietary fat intake. The aim of the present study was to examine the relation between depression and adipose tissue PUFAs of the n-3 and n-6 families in adults.

SUBJECTS AND METHODS

Subjects

In an attempt to evaluate the health and nutrition status of the lawyers of Iraklion county, Crete, Greece, it was agreed that all members of the lawyers association of the particular county would participate in a preventive medicine and nutrition program. The study sample consisted of 247 lawyers (146 males, 101 females), while the number of subjects with complete data on all variables was 139. The mean age was 39 years, while most of the subjects were 35 years of age. All subjects were informed about the nature and the purpose of this study and signed a consent form. The ethical committee at the University of Crete had previously approved the protocol of this research. The mean age of the group was 39 years. Subjects were interviewed by appointment at the Preventive Medicine and Nutrition Clinic of the University of Crete, where they underwent a thorough physical examination and clinical test. Data concerning dietary habits were collected using the 24 h dietary recall method.

Depression assessment

Depression level was assessed through the use of a Greek translation of the Zung Self-rating Depression Scale (ZSDS). ZSDS, a 20-item scale, has been reported to constitute a valid and reliable depression measure.

Anthropometric measures

Body weight was assayed by a digital scale (Seca) with an accuracy of ±100 g. Subjects were weighed without shoes, in their underwear. Standing height was measured without shoes to the nearest 0.5 cm with the use of a commercial stadiometer with the shoulders in relaxed position and arms hanging freely. Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m²).

Adipose tissue measures

Buttock subcutaneous tissue samples were collected by aspiration, using the method described by Beynen and Katan. The particular method has been reported to be rapid and safe, and to cause no more discomfort than a routine venipuncture. Buttock adipose tissue samples can be safely stored for up to 1.5 years without changes in the component fatty acids. Samples were taken from the left upper outer quadrant of the gluteal area, through the use of a 10-ml vacutaneous tube. Prior to aspiration, aspiration sites were sprayed with local anesthetic (ethyl chloride). Adipose tissue samples were stored in −80 °C. Prior to the analysis, samples were thawed and the fat was transferred to 10-ml screw-capped tubes with the aim of Pasteur pipettes and several drops (~0.5 ml) of chloroform: methanol (2:1, v/v). Methyl esters of the fat component fatty acids were prepared in the screw-capped vials according to the method described by Metcalfe et al. Briefly, 20–30 mg of fat sample was saponified with 0.5-ml NaOH in methanol and the FAME were prepared with 14% boron trifluoride in methanol following extraction with hexane after washing with saturated NaOH. The hexane (upper layer) containing the FAME was transferred to GC vials and stored at −20 °C until analysis. The FAME were separated on a 50 × 0.22 mm Id.BPX 70 fused silica capillary column, coated with 0.25 μm of cyanopropyl silicone provided by SGE (Melbourne, Australia), using a Hewlett-Packard (HP, Avondale, PA, USA) HP 6890 gas chromatograph equipped with an MSD-5972 mass ionization detector. The HP MS chemstation software was used for quantitation and identification of peaks. Baseline separation of over 50 FAME peaks was accomplished by means of mixed FAME standards (Sigma) and by reference to mass spectra library. The analytical conditions employed were as follows: volume...
injected 1 ml, carrier gas helium (1.0 ml/min), injector
temperature 230°C, MSD 280°C, split ratio 1:20–1:50
(depending on the sample quantity), and oven tempera-
ture from 120 to 245°C with stepped temperature
program: within a total run time of 40 min.

Data analysis
Data were analyzed through the use of the SPSS statistical
package. The statistical methods used were one-way
ANOVA, Pearson correlations and linear multiple stepwise
regression analysis.

RESULTS
Table 1 depicts means and standard deviations (SDs) of
depression, anthropometric, dietary and adipose tissue
fatty acid measures in the two genders, while Table 2
depicts means and SDs of the particular variables in
depressed vs non-depressed subjects. Depressed subjects
had significantly lower adipose tissue DHA (P<0.05).
Table 3 depicts Pearson correlations between depression and
adipose tissue fatty acids. Depression correlated
inversely with adipose tissue DHA (P<0.05) and c20:3
n-6 (P<0.05). The inverse relation between depression and
adipose tissue DHA was confirmed by stepwise
multiple linear regression analysis. Specifically, 3% of
the variability in Zung depression was significantly
accounted for by adipose tissue DHA (F=5.62, P<0.02)
(Table 4). Beta coefficient shows that adipose tissue DHA
related negatively to depression.

DISCUSSION
Given that adipose tissue fatty acid composition is a
biomarker of long-term (1–3 year) or habitual dietary fat

Table 1  Means and SDs. of depression, anthropometric, dietary and adipose tissue fatty acid measures in the two different genders

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th>Men</th>
<th></th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>N</td>
<td>Mean</td>
</tr>
<tr>
<td>Age</td>
<td>101</td>
<td>34.4</td>
<td>7.2</td>
<td>146</td>
<td>42.1</td>
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<tr>
<td>BMI</td>
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<td>23.4</td>
<td>3.4</td>
<td>145</td>
<td>29.2</td>
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<td>Dietary total fat</td>
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<td>81.3</td>
<td>36.5</td>
<td>146</td>
<td>88.7</td>
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<tr>
<td>Dietary caloric intake</td>
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<td>1725.1</td>
<td>627.4</td>
<td>146</td>
<td>1947</td>
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<tr>
<td>C18:2n6</td>
<td>80</td>
<td>11.9</td>
<td>2</td>
<td>123</td>
<td>10.9</td>
</tr>
<tr>
<td>C20:2n6</td>
<td>80</td>
<td>0.23</td>
<td>0.14</td>
<td>123</td>
<td>0.19</td>
</tr>
<tr>
<td>C20:3n6</td>
<td>80</td>
<td>0.24</td>
<td>0.14</td>
<td>123</td>
<td>0.28</td>
</tr>
<tr>
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<td>0.10</td>
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<td>0.40</td>
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<tr>
<td>Sum of n6 fatty acids</td>
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<td>1.35</td>
<td>0.33</td>
<td>123</td>
<td>1.41</td>
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<td>c18:3n3</td>
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<td>0.10</td>
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<td>0.48</td>
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<tr>
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<td>c22:5n3</td>
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<td>0.23</td>
<td>0.34</td>
<td>123</td>
<td>0.27</td>
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<tr>
<td>c22:6n3</td>
<td>80</td>
<td>0.20</td>
<td>0.14</td>
<td>123</td>
<td>0.29</td>
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<tr>
<td>Sum of n3 fatty acids</td>
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<td>0.96</td>
<td>0.30</td>
<td>123</td>
<td>1.14</td>
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<td>Depression (Zung scale)</td>
<td>73</td>
<td>33.4</td>
<td>7.6</td>
<td>92</td>
<td>30.5</td>
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</table>

Table 2  Means and SDs. of anthropometric, dietary and adipose tissue fatty acid measures in mildly depressed (Zung score > 40) v/s non-depressed subjects

<table>
<thead>
<tr>
<th></th>
<th>Non-depressed</th>
<th></th>
<th>Mildly depressed</th>
<th></th>
<th>Sig</th>
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<td></td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>N</td>
<td>Mean</td>
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<tr>
<td>Age</td>
<td>137</td>
<td>38.2</td>
<td>7.2</td>
<td>27</td>
<td>37.4</td>
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<tr>
<td>BMI</td>
<td>139</td>
<td>25.7</td>
<td>3.8</td>
<td>26</td>
<td>24.8</td>
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<tr>
<td>Dietary total fat</td>
<td>137</td>
<td>85.1</td>
<td>46.4</td>
<td>27</td>
<td>93.2</td>
</tr>
<tr>
<td>Dietary caloric intake</td>
<td>137</td>
<td>1817.2</td>
<td>819.1</td>
<td>27</td>
<td>2015.2</td>
</tr>
<tr>
<td>C18:2n6</td>
<td>121</td>
<td>11.2</td>
<td>1.5</td>
<td>22</td>
<td>11.5</td>
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<tr>
<td>C20:2n6</td>
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<td>0.14</td>
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<td>0.20</td>
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<td>0.22</td>
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<td>0.35</td>
<td>0.15</td>
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<tr>
<td>Sum of n6 fatty acids</td>
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<td>1.37</td>
<td>0.40</td>
<td>22</td>
<td>1.30</td>
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<tr>
<td>c18:3n3</td>
<td>121</td>
<td>0.48</td>
<td>0.07</td>
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<tr>
<td>c20:5n3</td>
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<td>0.07</td>
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<td>c22:5n3</td>
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<td>0.14</td>
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<td>0.22</td>
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<tr>
<td>c22:6n3</td>
<td>121</td>
<td>0.26</td>
<td>0.19</td>
<td>22</td>
<td>0.17</td>
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<tr>
<td>Sum of n3 fatty acids</td>
<td>121</td>
<td>1.04</td>
<td>0.33</td>
<td>22</td>
<td>0.97</td>
</tr>
</tbody>
</table>

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Nevertheless, mildly depressed subjects (ZSDS > 40)26 and none of the subjects exceeded the cutoff for moderate depression.9–13 However, no studies have been conducted on the relation between adipose tissue PUFA and depression. The present investigation is the first report on the relation between adipose tissue PUFA and depression. The fact that adipose tissue DHA accounted for only 3% of the variability in depression, in the present study, may stem from the fact that the majority of the subjects were non-depressed.11

The immune system has been reported both to be subjected to neural and neuroendocrine influence, and to exert a reciprocal regulation of neuroendocrine functions including HPA-axis activation.53 Certain cytokines appear to exert a stimulatory effect on HPA-axis and the production of CRF, cortisol and ACTH that are reportedly elevated in depression. For example, it has been reported that the HPA-axis activity is stimulated by cytokines such as IL-1,34 IL-633 and interferon-alpha (INF-α).54 It has been suggested that the stimulatory effects of IL-6 on HPA-axis activity are probably mediated through its membrane receptor (IL-6R). Both IL-6 and IL-6R along with their mRNAs have been identified in many brain regions.55 Both IL-1 and IL-6 have been reported to regulate the CRF-induced HPA-axis activation.56 Other

### Table 3
Pearson correlations between depression and adipose tissue fatty acids

<table>
<thead>
<tr>
<th>Depression (Zung scale)</th>
<th>C18:2n6</th>
<th>C20:2n6</th>
<th>c20:3n6</th>
<th>c20:4n6</th>
<th>Sum of n6 fatty acids</th>
<th>c18:3n3</th>
<th>c20:5n3</th>
<th>c22:5n3</th>
<th>c22:6n3</th>
<th>Sum of n3 fatty acids</th>
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<td>C18:2n6</td>
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<td></td>
<td></td>
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<tr>
<td>C20:2n6</td>
<td></td>
<td>-0.09</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>c20:4n6</td>
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<td>-0.09</td>
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<td></td>
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</tr>
<tr>
<td>Sum of n6 fatty acids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.14</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>c18:3n3</td>
<td></td>
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<td>-0.02</td>
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<td>-0.06</td>
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<td>c22:6n3</td>
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<td></td>
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<td>0.19</td>
</tr>
<tr>
<td>Sum of n3 fatty acids</td>
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<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td>-0.14</td>
</tr>
</tbody>
</table>

*P < 0.05.

### Table 4
Stepwise multiple regression analysis with depression as the dependent variable

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Predictor</th>
<th>Beta</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
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<td>Depression (Zung scale)</td>
<td>Adipose tissue c22:6n3</td>
<td>-0.20</td>
<td>-2.37</td>
<td>&lt;0.019</td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td></td>
<td>31.7</td>
<td>&lt;0.0005</td>
</tr>
</tbody>
</table>

Independent variables were age, sex, BMI, dietary total fat, dietary caloric intake, and adipose tissue c18:2n6, c20:2n6, c20:3n6, c20:4n6, sum of n6 fatty acids, c18:3n3, c20:5n3, c22:5n3, c22:6n3, and sum of n3 PUFAs.
cytokines such as INF-α and IL-2 also have been reported to stimulate CRF release from amygdala and hypothalamus.\(^57\) In addition to the brain, both IL-6 and its receptor are expressed on the adrenals.\(^58,59\) IL-6 has been reported to stimulate cortisol secretion from human adrenocortical cells in vivo\(^60\) and in vitro,\(^59,61\) in a time- and dose-dependent fashion.\(^58\) IL-6 stimulates the synthesis of both cortisol and ACTH.\(^60\) In addition to IL-6, other cytokines such as INF-β, INF-γ and tumor necrosis factor also have been reported to stimulate cortisol and ACTH release.\(^62\)

On the other hand, it has been reported that various antidepressive agents in vivo and in vitro reduce immune reactivity\(^63\) and that tricyclic antidepressants may inhibit cytokine production from human monocytes.\(^64\)

Moreover, administration of cytokines to cancer, multiple sclerosis and chronic hepatitis patients has led to depression, suicidal attempts and successful suicide. For example, IL-2 and INF-α administration to cancer patients led to increases in depression soon after initiation of treatment (3–5 days after)\(^65,66\) INF-β treatment for multiple sclerosis led to increases in depression in 41% of the patients treated, within 6 months after initiation of treatment.\(^67\) In another study, depression was induced by all four different types of INF-α tested on hepatitis C patients.\(^68\) There are consistent reports of increasing depression as a result of INF-α therapeutic regimens for cancer and viral hepatitis.\(^59–71\) In fact, of the studies reviewed, only one study reported no effect of INF-α treatment of hepatitis on depression.\(^72\) In addition to depression, IL-2 and INF-α therapies, particularly INF-α therapies, have been reported to have resulted in both suicidal attempts and successful suicide.\(^73–80\) Often, these attempts and successful suicide are not preceded by any prior psychiatric history.\(^73,76,77,79\) Psychiatric effects due to INF-α treatment are common and have frequently necessitated discontinuation of therapy, decreases in dose or antidepressant medication.\(^70\)

It has been reported that n-3 PUFA can suppress some of the pathophysiological features of depression, such as inflammation and immune reactivity markers. Specifically, in vitro studies have shown that EPA and DHA suppress IL-6 production by human endothelial cells.\(^81,82\) EPA and DHA have been reported to suppress the in vitro production of IL-1, IL-2, IL-6, TNF-α and INF-γ by human lymphocytes.\(^83\) Human studies have indicated that dietary supplementation with EPA and DHA results in suppression of IL-1, IL-2, IL-6 and TNF-α production by monocytes.\(^84–87\) Given that cytokines such as IL-1, IL-2, IL-6 and TNF-α have been reported to relate positively to depression, the observed negative relation between adipose tissue DHA and depression, in the present study, may stem from the inhibiting effect of DHA on the production of the particular cytokines.

In conclusion, in agreement with the findings of other studies, the observed negative relation between adipose tissue DHA and depression, in the present study, appears to indicate increasing long-term dietary DHA intakes with decreasing depression. This is the first literature report of a relation between adipose tissue DHA and depression. Given the positive relation between depression and cytokines, such as IL-1, IL-2, IL-6, INF-α and INF-γ, the observed negative relation between DHA and depression may stem from the inhibiting effect of DHA on cytokine synthesis.

**ACKNOWLEDGEMENTS**

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