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Fish consumption and severely depressed mood, findings from the first national nutrition follow-up study

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ABSTRACT

The evidence obtained from prospective studies to support the hypothesis that fish consumption may improve mental status remains limited. The current study prospectively assessed a low frequency of fish consumption as a risk factor for depressed mood. Included were 5068 adults aged 25–74 years examined in 1971–1975 as the baseline of the First National Health and Nutrition Examination Survey Follow-up Study. Frequency of eating fish at baseline was obtained using a 3-month food frequency questionnaire. Severely depressed mood (SDM) was defined as the Center for Epidemiologic Studies Depression Scale scores ≥22 or taking anti-depressants. After an average of 10.6 years of follow-up, among men ($n = 2039$), the percentage of individuals with SDM was 11.7%. Compared with frequent consumers (more than once a week), the odds ratios (ORs) were 1.43 (95%CI = 0.66–3.11) and 2.08 (1.08–4.09) respectively for the men eating fish once a week and less than once a week (p for trend = 0.03). Among women ($n = 3029$), the percentage of individuals with SDM was 17.89%. The ORs were 1 (reference), 0.91 (0.68–1.22) and 1.15 (0.83–1.59) respectively for the women eating fish more than once, once, and less than once a week. These estimates were obtained after adjustment for indicators of social deprivation and major physical diseases. The study concluded that independently from social deprivation and physical diseases, low fish consumption was a risk factor for SDM among men. Further studies are needed to confirm these findings and elucidate mechanisms for the difference between men and women.

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1. Introduction

In spite of the on-going controversy over the Food and Drug Administration's ruling that antidepressants will be labeled with a “black box” warning about the drugs' high potential suicide risk, the rule has fueled a searching for the natural antidepressant contained in dietary sources (Friedman and Leon, 2007; Antonuccio, 2008). There are converging evidences from ecological studies (Hibbeln, 1998; Hibbeln, 2002), cross-sectional analyses (Tanskanen et al., 2001; Zhang et al., 2005a; Raeder et al., 2007; Schins et al., 2007; Sontrop et al., 2008; Murakami, et al., 2010; Riemer et al., 2010), case control (De, Sr. et al., 2003; Sarri et al., 2008; Rees et al., 2009; Assies et al., 2010) and follow-up studies (Otto et al., 2003; Timonen et al., 2004; Sanchez-Villegas et al., 2007; Astorg et al., 2008; Akbaraly et al., 2009; Bountziouka et al., 2009; Colangelo et al., 2009; Golding et al., 2009), as well as randomized trials (Peet and Horrobin, 2002; Nemets et al., 2006; Su et al., 2008; Lesperance et al., 2010; Rondanelli et al., 2010), indicating that diets containing Ω-3 fatty acids, particularly fish and other seafood, may prevent depression and play a role in the prevention and treatment of mental disorder. The brain and central nervous system contain high concentrations of Ω-3 fatty acids, and a role of Ω-3 fatty acids in neurotransmitter synthesis, degradation, release, reuptake and binding has been demonstrated in biochemical studies (Levant et al., 2007; Su, 2009) and from animal models (Delion et al., 1996). Clinically, lower concentrations of Ω-3 fatty acids were observed in the plasma or red blood cell membranes of patients with psychological distress (Lucas et al., 2009a; Lucas et al., 2009b), and patients with a major depressive disorder (Edwards et al., 1998; Peet et al., 1998; Sarri et al., 2008; Gow et al., 2009) in comparison with controls, and depression severity has been found to correlate with the balance between Ω-3 and 18:3n-6 fatty acids in plasma (Tiemeier et al., 2003) and erythrocyte phospholipids (Maes et al., 1999) among patients. The magnetic resonance images revealed that, modest consumption of tuna/other fish, the prime source of Ω-3 fatty acids, was associated with greater gray matter volume (Conklin et al., 2007), and lower prevalence of subclinical infarcts and white matter

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; NHEFS, National Health and Nutrition Examination Survey I Epidemiology Follow-up Study; NHANES I, the first National Health and Nutrition Examination Survey; SDM, severely depressed mood.

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abnormalities among older adults (Virtanen et al., 2008). And most recently, using fluorodeoxyglucose positron emission tomography, a new modality of brain imaging, Sublette et al. observed that plasma levels of essential PUFA was correlated with regional human brain activity during a major depressive episode (Sublette et al., 2009). An autopsy study also demonstrated that docosahexaenoic acid (DHA) was the only fatty acid that was significantly different in the postmortem orbitofrontal cortex of patients with major depressive disorder relative to healthy controls (McNamara et al., 2007). The epidemiological evidence linking consumption of fish to depression, however, has not been consistent. Contrast to the studies reporting a significant association between depressive disorder and low Ω-3 fatty acids or infrequent fish consumption, a number of studies failed to observe this association(Hakkarainen et al., 2004; Miyake et al., 2006; Appleton et al., 2007a; Murakami et al., 2008; Strom et al., 2009; Suominen-Taipale et al., 2010; Poudel-Tandukar et al., 2011) or the therapeutic effectiveness of Ω-3 fatty acid supplements(Appleton et al., 2008; Freeman et al., 2008; Rees et al., 2008; Rogers et al., 2008; van de et al., 2008; Antypa et al., 2009; van de et al., 2009), leading researchers to suspect that the apparent associations observed mostly from ecological and cross-sectional studies may simply reflect an association between depressed mood and social deprivation and/or lifestyle (Appleton et al., 2007a; Appleton et al., 2007b; Strom et al., 2009; Suominen-Taipale et al., 2010; Poudel-Tandukar et al., 2011) or reverse causative effects of depressed mood (Freeman, 2010; Jacka et al., 2010). We took advantage of the prolonged follow-up experience of participants in the National Health and Nutrition Examination Survey I Epidemiology Follow-up Study (NHEFS) to prospectively assess the relationship of fish consumption to the subsequent development of depressed mood. The comprehensive baseline information of NHEFS provides an opportunity to control for the confounding effects from social deprivation and lifestyle.

2. Subjects and methods

2.1. Study population

Detailed descriptions of NHEFS have been published elsewhere (Madans et al., 1986a; Madans et al., 1986b; Ingram and Makuc, 1994; National Center for Health Statistics, 1997). In brief, the NHEFS was a study of adults aged 25–74 years who participated in the first National Health and Nutrition Examination Survey (NHANES I) from 1971 to 1975 ($n=14{,}407$). In the 1982–1984 follow-up survey, of the original NHANES I cohort, 15.1% were deceased, 7.1% were lost to follow-up, and 73% ($n=10{,}523$) of the participants were successfully traced and interviewed. The current study included the NHEFS participants who remained alive and had completed information on depressive symptoms assessed in 1982–1984 ($n=9517$). We excluded participants with 24-hour dietary recall coded as unsatisfactory ($n=70$), those with fish consumption missed from food frequency questionnaires ($n=2237$), those with information on alcohol drinking, cigarette smoking ($n=1779$) not available, and those with uncompleted data on socioeconomic status (SES), i.e. income level, education attainment, marital status, and type of residential area ($n=200$). Additional 163 participants were excluded due to an unavailability of body mass index (BMI), serum total cholesterol at the baseline, self-evaluated health status or the history of major physical diseases at the follow-up, leaving 5068 available for final analysis (Fig. 1).

2.2. Severely depressed mood (SDM)

Depressed mood was assessed in the 1982–1984 follow-up survey using the Center for Epidemiologic Studies Depression Scale (CES-D) questionnaire. The CES-D questionnaire was developed for epidemiologic surveys of the general population to measure depressive feelings and behaviors during the past week (Weissman et al., 1977). It consists of 20 descriptive statements of depressed mood, feelings of worthlessness, hopelessness, and loneliness; loss of appetite; sleep disturbances; concentration problems; and psychomotor retardation. Participants were asked to rate each item according to the frequency experienced in the past week and scored on a standard 4-point scale from 0 to 3. The 20 items had a potential range of 0–60, with the higher scores representing responses in the depressed range. Only persons who answered all 20 items on the questionnaire were included in the current analysis. Those with a total score on the CES-D ≥16, which corresponds approximately to the 80th percentile score, were considered to have severely or moderately depressed mood. A cut-off ≥22 has also been used as an indicator of severely depressed mood in previous studies (Husaini, 1980; Zhang et al., 2005b; Celentano et al., 2008). In the preliminary analyses, we observed that CES-D ≥16 as the cut-off was not able to identify distinct levels of severity of the symptoms and provide adequate statistical power to detect the association. We finally categorized participants as having SDM and not using the cutoff CES-D ≥22. The individuals who were taking anti-depression medication when the follow-up interview was conducted ($n=143$) were also included as having SDM. Sensitivity analysis using cutoff CES-D ≥16 was also performed.

2.3. Fish consumption

A 3-month food frequency questionnaire was administered at the baseline survey (1971–75) by trained interviewers, usually registered dietitians. The questionnaire covered the 3 months prior to the interview and referred to usual consumption excluding periods of illness or dieting. Information was collected on 18 groups ingested daily and/or weekly in the usual pattern accounting for all regular meals eaten as well as for between meal foods or snacks, Monday through Sunday, including holidays. The interviews were conducted in specially designed mobile examination units. On-site evaluations, review of questionnaires, and taped interviews were conducted as part of the data quality control, only dietary records coded as satisfactorily completed by interviewers were used in this analysis. The primary item used in this investigation asked participants "how often fish or shellfish was eaten in the past 3 months, excluding periods of illness or dieting?" The choices of the response available in the original questionnaire were, never, less than once a week, one to six times per week, one to two times per day, and unknown. Categories of fish consumption used in the current analysis were selected to identify distinct levels of consumption and to provide adequate numbers at risk in each level. Three categories of consumption frequency were analyzed: less than once a week (including never), once a week, and more than once a week.

2.4. Covariates

Covariates included socioeconomic status (SES) or social deprivation indicators, behavioral and dietary characteristics at the baseline, self-evaluated health status and the specific medical condition at the follow-up. Since more than 90% of the samples were whites, ethnicity was simply coded as whites and others. Education attainment at baseline was measured as the highest completed grade of school. Marital status was

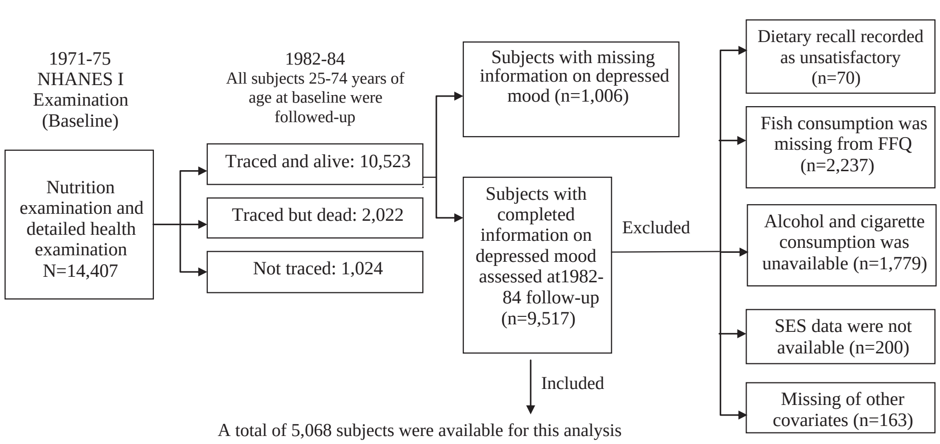

Fig. 1. Flow chart of the study population included.

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collapsed into two categories: married and others. Poverty status was defined by the ratio of family income to the federal poverty line threshold established annually by the US Bureau of the Census. Other SES or social deprivation indicators included employment status [unemployed, currently employed, house-keeping, others (including student, retired, and being unable to work)], occupation (farm, non-farm), and types of residence area (urban, suburban and rural) at baseline.

The category for alcohol consumption separated heavy (every/just about every day) and moderate drinkers (two to three times a week) from less regular drinkers (once a week or less) or non-drinkers. Information on smoking status was obtained in 667 participants who underwent a more detailed baseline examination in 1971. For the remaining participants, information on smoking status at baseline was derived from responses to questions on lifetime smoking history obtained at their follow-up interviews between 1982 and 1984 or later. The participants were classified as "having smoked more than 100 cigarettes in a life-time", or otherwise as "not". At the follow-up survey, the respondents were asked "Has a doctor ever told you that you had any of the following conditions?", this was followed by a list of 39 chronic and acute conditions, some described with vernacular expressions. The most frequently reported conditions included arthritis, fractures, bladder infections, and anemia, but we selected the conditions of cancer, stroke, heart attack and diabetes as potential confounders. A self-evaluated health indicator with categories of excellent, very good, good, fair, and poor was recoded as "excellent" "very good or good" and "poor or fair" to reduce the likelihood of over-specification of regression models. Dietary energy intakes, calories from fat and daily consumption of cholesterol were estimated using the 24 h recall method. The 24-h dietary recall, administered by the same trained staff prior to beginning the frequency questionnaire, provided such information as specific food items and their quantities ingested for all regular meals, between meal foods or snacks consumed on that day, midnight to midnight, preceding the interview for each participant interviewed. All food ingested during the 24-h period was then reduced by a computer program to standard units of measure for actual dietary intake during 24-hour recall period, and total dietary energy ingested in 24 h was estimated accordingly. The 3-month food-frequency questionnaire also included three items referring to fruit and vegetable intake. The item used in this investigation asked participants how often "fruits and vegetables of all kinds fresh, canned, frozen, cooked, or raw, and juices" were usually consumed in the past 3 months, excluding periods of illness or dieting. Frequency of consumption of fruit and vegetables was grouped into four categories by intake (<1 time/day, 1 time/day, 2 times/day, and ≥3 times/day).

2.5. Statistical methods

Because the NHANES I design involved stratification, several levels of clustering, and special weighting of selected age and race groups, SUDAAN (SAS-callable) software from Research Triangle Institute accounting for NHANES sampling methods was conventionally utilized. Hazard ratios derived from Cox proportional hazard regression would be preferable given the cohort design of the current study. However, we present the odds ratios (ORs) obtained from a typical logistical regression due to these considerations. The CES-D scale was designed to identify individuals with current depressed mood, and was not able to measure past episodes, therefore, it is impossible to pinpoint the first date of onset after the baseline survey, and we have to assume that the date of follow-up survey as the onset date of the current depressive episodes if SDM presented. Consequently, the follow-up durations were relatively unified for the entire cohort regardless of the depression status, with an average being 10.6 years (ranging from 8.0 to 12.5 years). The outcome variables by nature can be defined as 'the trait of depressed individuals' rather than 'the state of depressed mood'. Because the percentage of individuals with SDM in the study population was higher than 10%, overestimation may occur with ORs derived from the logistic regression (Zhang and Yu, 1998). The estimates derived from the logistic regression in the preliminary analyses, however, were almost identical to those obtained from the Cox proportional hazard analyses. Therefore, we presented the estimates from logistic regression only with the status of SDM (yes/no) as the dependent variables. We did not use the −2 log likelihood test to simplify the regression models; instead, all potential confounders were retained in the final multivariable models. Separate analyses were performed for each gender. To assess the mediating or confounding effects from social deprivation and behaviors or other dietary factors other than fish consumption, we conducted hierarchy analyses according to the methods discussed by Baron, Kenny (Baron and Kenny, 1986) and Holmbeck (Holmbeck, 1997). The strengths of the association between fish consumption and SDM are reduced when mediating variables or confounders are included in the model than when they are not included.

3. Results

The average follow-up period was 10.61 years for both men ($n = 2039$) and women ($n = 3029$) (data not shown). The mean of CES-D score assessed at the follow-up was higher among women than men; and 32 men and 111 women were taking anti-depressants when the follow-up interviews were conducted. Overall, 17.89% ($n = 237$) of women and 11.75% ($n = 562$) of men were identified as with SDM. Significant differences were observed between genders for most characteristics at baseline. The percentages of participants eating fish less than once a week were 43.78 and 38.14 respectively for men and women. Women were more likely to be socially deprived, i.e., living under poverty line, being less educated or unemployed.

When the study population was further stratified by the levels of fish consumption within each gender (Table 1), the percentage of men with SDM was significantly lower among individuals who ate fish one or more times a week than among the individuals who never ate fish or ate less than once a week, but no such a difference was observed from women. For both genders, the individuals who ate fish less frequently were less educated and more likely to live below poverty. It was also noted that, compared with individuals who never or rarely ate fish, the frequent fish consumers were less likely to be smokers among men, but more likely to be alcohol drinkers among women.

The percentage of participants with SDM was almost double (14.20%) in men who ate fish less than once a week or never compared with men eating fish more than once a week (8.25%, Table 2). Using men who ate fish more than once a week as the referent group, we obtained ORs of 1.30 (95%CI = 0.66–2.54) and 1.84 (1.01–3.36) respectively for men eating fish once a week and less than once a week or never after adjustment for age. Further controlling for indicators of social deprivation and health behaviors did not diminish the association. Instead, the OR for men who ate fish less than once a week or never was increased to 2.08 (1.08–4.09). The p for trend test was 0.0336. No significant association between the frequency of eating fish and the risk of SDM was observed among women, either from crude or adjusted ORs.

In the sensitivity analyses, we investigated the potential biases introduced by the choice of CES-D cut-off to define the SDM by repeating analyses using a cut-off ≥16 instead of 16. All of the principal findings were retained but less significant largely due to the misclassification associated with decreased specificity. The ORs were 1.10 (0.72–1.68) and 1.18 (0.74–1.89) respectively for men eating fish once a week and less than once a week or never compared with men eating fish more than once a week. No linear correlation between fish consumption and CES-D scores was observed in additional analyses using CES-D as a continuous variable, indicating a potential threshold effect of CES-D.

4. Discussion

Using a national cohort, we found a significant dose–response protective effect of fish consumption against SDM among men. The effect persisted after adjustment for the indicators of social deprivation, general health, dietary, smoking, drinking and other behavioral characteristics, and major health conditions. The protective effect against SDM did not exist among women. The results of this work, in principle, are consistent with the conclusions from previous ecological (Hibbeln, 1998; Hibbeln, 2002), cross-sectional (Tanskanen et al., 2001; Zhang et al., 2005a; Raeder et al., 2007; Schins et al., 2007; Murakami, et al., 2010; Riemer et al., 2010), case control (De, Sr. et al., 2003; Sarri et al., 2008; Rees et al., 2009; Assies et al., 2010), and follow-up studies (Otto et al., 2003; Timonen et al., 2004; Sanchez-Villegas et al., 2007; Astorg et al., 2008; Akbaraly et al., 2009; Bountziouka et al., 2009; Colangelo et al., 2009; Golding et al., 2009), as well as randomized trials (Peet and Horrobin, 2002; Nemets et al., 2006; Sontrop et al., 2008; Su et al., 2008; Lesperance et al., 2010; Rondanelli et al., 2010) with study populations ranging from children(Nemets et al., 2006), adolescents (Murakami et al., 2010) to the elderly (Bountziouka et al., 2009; Rondanelli et al., 2010). However, increasing numbers of studies failed to support the association from cross-sectional studies(Miyake et al., 2006; Appleton et al., 2007a; Appleton et al., 2008; Murakami et al., 2008; Suominen-Taipale et al., 2010), cohort follow-ups (Hakkarainen et al., 2004; Strom et al., 2009; Poudel-Tandukar et al., 2011) and randomized clinical trials(Freeman et al., 2008; Rees et al., 2008; Rogers et al., 2008; van de et al., 2008; Antypa et al., 2009; van de et al., 2009) as well. The cross-sectional studies have been categorized as descriptive research and have limited values in assessing the directions of the

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Table 1
Socio-demographic, behavioral and physical characteristics by gender, 5068 adults aged 25–74 years, NHEFS, 1971–1982[a].

Characteristics of participants	Men ($n=2039$)			Women ($n=3029$)		
	<1 week	1/week	>1 week	<1 week	1/week	>1 week
Follow-up time, year (mean)	10.7 (0.1)	10.57 (0.13)	10.44 (0.14)	10.7 (0.1)	10.6 (0.1)	10.6 (0.1)
CES-D score, mean (at follow-up survey)	14.0 (0.3)	13.85 (0.25)	13.57 (0.44)	15.7 (0.3)	15.2 (0.2)	15.2 (0.3)
CES-D score ≥22 (at follow-up survey)	12.0 (1.3)	8.49 (1.08)*	7.16 (2.00)*	17.5 (1.6)	13.6 (1.2)	14.9 (1.6)
Taking anti-depressant (at follow-up)	2.5 (0.5)	2.68 (0.95)	2.49 (0.68)	5.5 (1.1)	2.9 (0.6)	3.7 (0.9)
Socio-demographic characteristics						
Age, years (mean)	42.7 (0.4)	44.54 (0.4)	43.73 (0.8)	43.30 (0.4)	43.45 (0.5)	44.9 (0.6)
Non-Hispanic white	93.0 (1.5)	92.95 (1.2)	89.57 (2.1)*	92.98 (0.8)	89.79 (1.2)	89.2 (1.5)*
Living below the poverty line	22.4 (1.9)	19.20 (1.6)*	16.72 (2.1)**	26.73 (1.9)	25.58 (1.6)	23.6 (2.1)
Center city of metropolitan	28.5 (2.2)	28.30 (2.6)	34.13 (3.7)	28.95 (1.8)	30.14 (2.3)	28.6 (2.8)
Some years of high school or below	33.1 (1.5)	30.91 (2.0)**	29.26(3.2)**	33.74 (1.8)	28.64 (1.9)	25.7 (2.5)*
Never married	12.00 (1.7)	7.51 (0.9)**	13.69 (2.4)	22.53 (1.5)	22.52 (1.6)	23.6 (2.4)
Employed[b]	89.3(1.1)	89.19 (1.3)	87.66 (1.8)	40.81 (1.8)	42.12 (1.6)	49.3 (2.7)
Behavioral and dietary characteristics						
Dietary intake of calories, kJ/24 h (mean)	10,043 (208)	10,019 (237)	10,826 (364)	6,254 (116)	6,631 (140)	6,792 (209)
Saturated fatty acids, g/24 h (mean)	3,912 (97)	3,659 (105)	3,656.6 (134)	2,314 (54)	2,358 (49)	2,270 (96)
Cigarette smoking, 100+/lifetime	80.5(1.9)	78.4(1.9)	74.5(3.2)*	57.7 (2.0)	56.9 (1.90)	53.66 (2.5)
Alcohol drinking, every or just every day	23.3 (1.7)	29.3 (2.4)*	24.8 (3.3)	10.3 (1.6)	9.9 (1.2)	14.3 (2.3)*
Poor self-evaluated health status	20.8(1.8)	16.8 (1.7)	16.1 (2.9)	18.6 (1.8)	15.1 (1.5)	14.6 (1.8)
Normal body mass index (18.5–24.9 kg/m^2)	41.8 (2.3)	39.0 (2.2)	43.4 (3.2)	62.5 (1.7)	58.0 (1.7)	54.3 (2.7)**
Total serum cholesterol, mg/dL (mean)	215(2)	223(2)	221 (3)	220 (3)	217 (2)	221(3)
Physical diseases assessed at follow-up survey						
Cancer	3.26 (0.8)	2.63 (0.7)	2.33 (1.1)	4.2 (0.8)	3.68 (0.7)*	5.16 (0.9)
Stroke	1.11 (0.8)	1.74 (0.5)	0.85 (0.5)	0.6 (0.3)	0.59 (0.2)	0.49 (0.3)
Heart attack	6.77 (0.8)	8.55 (1.1)	7.53 (2.3)	1.4 (0.4)	3.23 (0.6)	2.61 (1.1)
Diabetes	6.35 (0.9)	6.27 (0.8)	7.93 (2.0)	4.2 (0.7)	4.97 (0.8)	4.93 (1.1)

Abbreviations: NHEFS, National Health and Nutrition Examination Survey I Epidemiologic Follow-Up Study; CES-D, Center for Epidemiologic Studies Depression Scale.
[a] Values were calculated using the 1971–75 survey sampling weights and reported as percentage (standard error) unless otherwise indicated. The characteristics were assessed at the baseline survey (1971–75) unless otherwise indicated. The *p*-values were generated from Cochran–Mantel–Haenszel test for categorical variables and *t*-test for continuous variables.
* *p*-value<0.05 (0.05/3, Bonferroni adjusted test), and reference level was the group with fish consumed less than once a week.
** *p*-value<0.017 (0.05/3, Bonferroni adjusted test), and reference level was the group with fish consumed less than once a week.
[b] Housing-keeping was categorized as a separate group other than unemployed.

associations under investigation. Whether low fish intake occurred before depressive mood or depressive mood decreased appetite and therefore caused infrequent consumption of fish are beyond the scope of cross-sectional studies. The most relevant contrary evidences, therefore, came from cohort studies and randomized clinical trials. Nested within a randomized cancer prevention trial of alpha-tocopherol and beta-carotene (ATBC trial), a cohort of 29,133 men demonstrated no associations between the dietary intake of Ω-3 fatty acids or fish consumption and depressed mood, major depressive episodes after more than 6 years of follow-up (Hakkarainen et al., 2004). It was, however, unclear how systemic oxidant stress due to tobacco use counteracted, and how anti-oxidative effect from alpha-tocopherol and beta-carotene given to the subjects antagonized the expected benefit from Ω-3 fatty acids in the ATBC trial (Astorg, 2005). A potential detrimental role of mercury relatively high in Nordic freshwater fish might be a part of the explanation for the lack of protection from fish consumption observed in the ATBC cohort study. Although the data from Danish and Japanese cohorts did not show substantial evidence to support the association, "a higher risk of postpartum depression was found for the lowest compared with the highest fish intake group" in Danish National Birth Cohort (Strom et al., 2009), and "a significantly increased risk of suicidal death was observed among women with very low intake of fish, with HRs for those in 0–5th percentile versus middle quintile of 3.41 (1.36–8.51)" from the Japan Public Health Center-based Prospective Study (Poudel-Tandukar et al., 2011). The strongest contrary evidences against the postulated association between Ω-3 fatty acids and depressive mood might be the fact that a number of randomized clinical trials did not favor the hypothesis (Silvers et al., 2005; Grenyer et al., 2007; Rogers et al., 2008). However, it was suggested that using olive oil as the placebo might be part of the reason of failure to obtain an effectiveness of Ω-3 fatty acids supplements against depressive mood. In these trials with olive oil as the placebo (Silvers et al., 2005; Grenyer et al., 2007; Rogers et al., 2008), both treatment groups showed significant and sustained improvements in depressive symptoms, suggesting that strong placebo effects were operating. There might have been some effects from both olive oil and fish oil, or general expectations (Zhang and Li, 2008).

The remarkable discrepancy of the results between the current study and the previous work which observed an association between fish consumption and depression is the gender difference. The previous studies found that the association, if presented among study population with both men and women included, was more salient among women than men (Timonen et al., 2004; Sontrop et al., 2008; Colangelo et al., 2009; Li et al., 2009; Rondanelli et al., 2010; Poudel-Tandukar et al., 2011). In contrast, we observed an association among men, so did Astorg et al. (2008), Murakami et al. (2010) and Murakami et al. (2008). Gender differences in neurotransmitter and phospholipid metabolism have been discussed to explain the gender-specific association (Timonen et al., 2004). Depressive disorder is more heritable in women compared with men (Bierut et al., 1999; Kendler et al., 2001). Therefore, environmental factors, including dietary intake, may contribute relatively less to the development of depressed mood in women. Animal studies have demonstrated that females have a better reserve of essential fatty acids in body than males under conditions of low intake or deficiency, and males are more sensitive to deficiency of essential fatty acids compared with females (Greenberg et al., 1950; Huang and Horrobin, 1987). Similarly, men may be more sensitive to dietary intake of Ω-3 fatty acids under condition of deficiency. Smoking is known to decrease omega-3 levels but only if currently smoking (Sontrop et al., 2008). The prevalence of current smokers was higher in men than in women, which may further increase Ω-3 fatty acids deficiency, and increase the men's sensitivity to dietary intake of Ω-3. We don't think that the difference of the percentages taking fish oil supplements between men and women at the follow-up interview contributed to the gender

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Table 2
The odds of severely depressed mood associated with the frequency of fish consumption 5068 adults aged 25–74 years, NHEFS, 1971–1982.

	Severely depressed mood[a]			Odds ratio (95% CI) adjusted for[b]		
	Sample size[c]	% of case	SE of %	Age	Age, socioeconomic status	All covariates
Men (n = 2039)						
More than once a week	309	8.25	2.21	1	1	1
Once a week	826	10.43	1.24	1.30(0.66–2.54)	1.41(0.70–2.84)	1.43(0.66–3.11)
Less than once a week	904	14.20	1.52	1.84(1.01–3.36)	1.85(1.00–3.42)	2.08(1.08–4.09)
p for trend				0.05	0.05	0.03
Women (n = 3029)						
More than once a week	556	17.09	1.80	1	1	1
Once a week	1,255	15.93	1.30	0.92(0.77–1.24)	0.89(0.66–1.20)	0.91(0.68–1.22)
Less than once a week	1,218	20.46	1.74	1.24(0.90–1.71)	1.16(0.83–1.62)	1.15(0.83–1.59)
p for trend				0.19	0.38	0.40

Abbreviations: NHEFS, National Health and Nutrition Examination Survey I Epidemiologic Follow-Up.
[a] The severe depressed mood was defined as CES-D score ≥ 22 and/or taking anti-depression medicine.
[b] The variables of socioeconomic status included race/ethnicity, education attainment, family income level, marital status, types of residence area, occupation, and employment status assessed at the baseline. Other covariates included body mass index, alcohol drinking, cigarette smoking, serum total cholesterol, total dietary energy intake, saturated fatty intake, frequency of eating fruit and vegetables assessed at the baseline survey, and self-evaluate health status and the history of major physical diseases (cancer, diabetes, stroke and heart attack) assessed at follow-up survey.
[c] The sample sizes and the numbers of individuals with SDM were presented as un-weighted but the percentages were estimated as weighted using appropriate weighting and nesting variables.

difference of the association since the percentages of individuals taking fish oil were low for both men and women, 0.62 and 2.22% respectively (data not shown). However, we are not able to rule out the possibility that gender-specific misreporting in respect to social desirability and social approval of dietary pattern and eating behaviors caused the difference observed between men and women.

A number of reviews published recently have provided an excellent summary of the theoretical basis for the possible effect of fish consumption or Ω-3 fatty acids on mood and depression (Otto et al., 2003; Appleton et al., 2006; Parker et al., 2006; Orr and Bazinet, 2008; Owen et al., 2008; Stahl et al., 2008; Liperoti et al., 2009; Martins, 2009; Su, 2009; Lin et al., 2010). In brief, consumption of fish may be able to bring changes in the phospholipid composition of cell membranes, alter membrane microstructure and the function of membrane-associated proteins. In addition to the direct effects of ω-3 fatty acids derived from fish, high fish consumption may also indicate a healthier diet and better nutritional status with respect to essential nutrients in general. Therefore, researchers suspected that the inconsistency from previous studies might reflect the confounding effects from the association between low fish consumption and social deprivation and unhealthy lifestyle, including dietary pattern (Appleton et al., 2007a). By controlling for an array of covariates, the current study was able to demonstrate that the association was not entirely due to confounding effects, and fish consumption may be related to a low risk of being depressed independently.

Limitations of the current study included possible bias caused by loss to follow-up and missing data on baseline survey. The majority of the persons who died, were lost to follow-up or excluded due to missing covariates were the persons with low SES or the elderly, and these groups were more vulnerable to detrimental effects from environmental risk factors (Madans et al., 1986a; Madans et al., 1986b; Ingram and Makuc, 1994). Therefore, the bias, if any, should lead to an attenuated OR toward unity. Use of a single food frequency questionnaire survey may introduce errors due to daily or seasonal variability of dietary pattern. Dietary practices may also have changed during the 10-year follow-up period. Therefore, repeated measures were desirable for accurate dietary assessments. However, the repeated dietary recalls in NHEFS were conducted simultaneously in 1982–1984 when mood was measured, reducing the values of temporality assessment. It is impossible to rule out the reverse causation from the data collected cross-sectionally. Change in eating habits is a well-identified sign of depression, and depressive symptoms have been well known to be associated with eating pathology (Wildes et al., 2005). It's highly possible that the depressed individuals changed their dietary behaviors and ate less fish rather than eating less fish caused depressive mood. Therefore, the current study kept its prospective nature and did not mix with cross-sectional analyses. In addition, The CES-D scale is not accurate in measuring past episodes (Breslau, 1985) and nor in identifying individuals with major mood disorder. Major mood disorder has been previously shown to be most closely related to Ω-3 intervention in clinical trials (Appleton et al., 2006; Schiepers et al., 2009). Only a portion of the NHEFS participants were invited for a more detailed medical examination at baseline, disabling us from excluding the individuals with a history of psychiatric disorder. Lack of information on leisure-time physical activity was also a concern. Our study had strengths as well. Our data came from a nationwide longitudinal survey with 10 years of follow-up, and the most important confounding variables, such as SES, health-status, and lifestyle variables, were controlled for, therefore, the conclusion is relatively generalizable.

In conclusion, we observed an association between SDM and low consumption of fish among men but not among women. Given the metabolic and psychiatric side effects of some psychotropic medications and various design limitations existing in previous trials (Appleton et al., 2006), and the current one, we are calling for additional well-designed trials with adequate power to assess the clinical effectiveness of marine products for prevention and treatment of psychiatric disorders. Clarifying the biological and behavioral pathways involved and examining the difference between men and women are of particular interests for future biological studies.

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