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**Longitudinal associations of fish consumption and depression in young adults**

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Abbreviations:

BMI: Body mass index

CDAH: Childhood Determinants of Adult Health

CIDI: Composite International Diagnostic Interview

Running head: Fish consumption and depression

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Few studies have examined longitudinal associations between fish consumption and depression; none have defined depression using a diagnostic tool. This study investigated whether fish consumption was associated with fewer new depression episodes in a national study of Australian adults. In 2004-06, 1,386(38% male) 26-36 year olds completed a 127-item (nine fish items) food frequency questionnaire. Fish intake was examined continuously (times/week) and dichotomised (reference group <2 times/week). During 2009-11, the lifetime version of the Composite International Diagnostic Interview was administered by phone interview. New depressive episodes of major depression/dysthymic disorder, since baseline, were defined using the Diagnostic and Statistical Manual of Mental Disorder, fourth edition (DSM-IV). During follow-up 160(18.8%) women and 70(13.1%) men experienced depression. For women, each additional serve of fish consumed per week at baseline decreased the risk of having a new depressive episode by 6% (adjusted relative risk:0.94; 95% confidence interval:0.87,1.01). Women who ate fish ≥2/week at baseline had a 25% lower risk of depression during follow-up than those who ate fish <2/week (adjusted relative risk:0.75, 95% confidence interval:0.57,0.99). Reverse causation was also suggested but appeared to be restricted to those with recent depression. Fish consumption was not associated with depression in men. These findings provide further evidence that fish consumption may be beneficial for women's mental health.

Key words: fish, depressive disorder, diet, longitudinal study.

Depression affects approximately 340 million people worldwide and is the second leading cause of years lived with disability (1). The onset of depression increases with age through adolescence, with the highest prevalence in young adulthood (2). Due to low compliance with antidepressant medications and some undesirable side effects (3), there is increasing interest in how modifiable lifestyle factors may help prevent depression (4).

There is emerging evidence that fish and fish oils are beneficial for mental health. In cross-sectional studies, the prevalence of depression is lower in countries with higher apparent fish consumption (5) and among individuals with higher fish intake (6-13). Interestingly, studies that have stratified the analyses by sex have reported significant associations in only women (7,8) or only men (13). Some cross-sectional studies reported no association between fish consumption and depression (14-16). Very few longitudinal studies exist. In a national study of 5,068 adults aged 25-74 years from the USA, baseline fish consumption appeared protective against severely depressed mood 10 years later among men but not women (17). However, depression was assessed using a screening tool not a diagnostic tool, which may overestimate the effect estimate.

Omega-3 fatty acids are the component of fish believed to be beneficial for mental health. Individuals with depression tend to have lower serum omega-3 fatty acids concentrations than those without depression (18). In a recent study of French adults, lower intake of omega-3 polyunsaturated fatty acids (PUFA) was associated with less depressive symptoms in men at baseline but not with incident depression at the 13 year follow-up (19).

A recent meta-analysis of randomised controlled trials showed omega-3 supplementation was associated with a decline in depressed mood. However, there was evidence of publication bias (20). Trials published since this review have shown that supplementation

with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) has benefits for depressive symptoms in menopausal women and older adults (21-25). Supplementation with fish oil has limitations as components of fish other than omega-3 fatty acids may be beneficial for mental health, or may be synergistic.

Major limitations of previous studies are the cross-sectional design and measures of depression which have relied on self-report or screening tools rather than diagnostic instruments. As benefits may only be evident in more severe depression (20), diagnostic specificity is important. Longitudinal studies provide stronger evidence for causation than cross-sectional studies. However, the few studies that have prospectively examined associations between fish consumption and onset of depression have not investigated the possibility of reverse causation eg. whether there is an association between depression at baseline and fish consumption at follow-up. This is important because changes in appetite are a common symptom of depression (26). Most studies have not adjusted for important confounding factors such as physical activity and healthier diets (20), which are known to be associated with fish consumption (27). The current study overcomes these limitations.

Using a large population-based national sample of Australian adults, this study aimed to examine longitudinal associations between fish consumption and onset of depression, defined using a diagnostic tool. We also investigated whether depression was prospectively associated with a lower intake of fish.

**METHODS**

The Childhood Determinants of Adult Health (CDAH) study is a follow-up of the 8,498 children who participated in the 1985 Australian Schools Health and Fitness Survey, a nationally representative sample of 7-15 year old school children (28). During 2002-04, 6,840

participants were traced and 5,170 agreed to participate in the CDAH study (Figure 1). During 2004-06, when the participants were 26-36 years old, 2,881 participants completed questionnaires and 2,410 participants also attended one of 34 study clinics that were held in each state and territory of Australia for physical measurements (CDAH-1, referred to as baseline). The second follow-up (CDAH-2) was conducted during 2009-11, when the participants were 31-41 years old. Participants completed a postal questionnaire and a computer-assisted telephone interview (N=1,548). The Southern Tasmanian Health and Medical Ethics Committee approved the study. Written informed consent was obtained at both time points.

Fish consumption

Diet was assessed at both time points using a 127-item food frequency questionnaire and a food habits questionnaire. The food frequency questionnaire was a modified version of the one used in the 1995 National Nutrition Survey and was based on an existing validated questionnaire developed for Australian populations (29). The number of fish items was increased to reflect current consumption patterns. Nine fish and seafood items were included (canned fish, fresh fish, frozen fish, fried fish, mussels/oysters, lobster/crayfish/yabbies, calamari/squid, prawns, other seafood). Participants were asked to estimate their intake over the previous 12 months by choosing one of nine response options, ranging from “never/less than once per month” to “six or more times per day”. Weekly equivalents were calculated for each item, assuming one serve was consumed at each eating occasion (29). Total weekly fish consumption was calculated by summing the weekly equivalents for all fish and seafood items. Participants were excluded from the analysis if they did not answer all of the fish items (n=79) because it was not known if they missed that

item or did not consume it. The exception was if they were only missing “other seafood” (n=27) as the “other” item at the end of each section was commonly skipped (eg. number of participants missing “other” items was up to 214 for “other vegetables”).

## Depression

During CDAH-2, participants completed the life-time version of the Composite International Diagnostic Interview (CIDI_Auto 2.1) as a computer-assisted telephone interview (26). The CIDI was developed for use by trained non-clinical interviewers in a range of different community populations. Computerised diagnostic instruments have been shown to be more reliable, comprehensive and to have lower bias than routine clinical interviews (30). The lifetime version of the CIDI provides age of first onset and the age of the most recent episode. Age of most recent episode was used to determine whether an episode of depression or dysthymia had occurred since CDAH-1. Participants who experienced an episode of major depression/dysthymic disorder (here on referred to as depression) defined by the Diagnostic and Statistical Manual of Mental Disorder, fourth edition (DSM-IV), since baseline, were compared to those who did not. The prevalence of lifetime depression in the study sample was compared with that in the general Australian population.

## Covariates

Socio-demographic variables were self-reported at baseline and included age, marital status, education, and employment status. Accessibility/Remoteness Index of Australia (ARIA) classifications (major city, inner regional, outer regional/remote) were assigned to participants based on residential address and census collection districts. Smoking status and medication use was self-reported. For women, parity was defined as the number of live births.

The number of standard alcoholic drinks (10g alcohol) consumed per week was estimated from nine alcoholic beverages in the food frequency questionnaire and their average alcohol concentration. Usual fruit and vegetable consumption were assessed using short questions (29). Information from the food frequency and food habits questionnaires was used to assess diet quality using a dietary guideline index, based on the Australian Guide to Healthy Eating (31). The score included 15 components that were scored from 0-10, with 10 indicating optimal intake (total range 0-150). Proportional scores were given for participants who consumed intermediate amounts. This score has been shown to be a valid measure of diet quality (32,33). The food frequency questionnaire also asked about supplement use including fish oil/evening primrose oil supplements (the question combined these two supplements) and included questions on use of omega-3 fortified margarine for cooking and as a spread on breads and savoury biscuits. Leisure time physical activity and time spent sitting were assessed using the long version of the International Physical Activity Questionnaire (IPAQ) (34).

During CDAH-1, weight and height were measured at study clinics using a portable scale (Heine, Dover, NH, USA) and stadiometer (Invicta, Leicester, UK). Participants who did not attend a study clinic self-reported their height and weight and a correction factor was applied (35). BMI was calculated ($kg/m^2$). Health status was assessed using the SF12 (36).

Statistical analyses

Baseline fish consumption was treated as a continuous exposure variable (times/week), and also dichotomised with <2 times/week as the reference group. This cut point was chosen to reflect current recommendations by the National Heart Foundation of Australia and the American Heart Association, to eat fish at least two times/week. Relative risks were

calculated using Poisson regression with robust standard errors. Reverse causation was examined by investigating whether depression since baseline was associated with fish intake at the CDAH-2 survey. Covariates included in the analyses were factors significantly associated with having depression since baseline in the univariable analysis. Men and women were analysed separately because previous studies suggest sex differences in the relationship between fish consumption and depression (7,8,13).

Sensitivity analyses were conducted taking into consideration fish consumption at baseline and follow-up in order to provide a longer term estimate of fish intake. The analysis was also repeated excluding those who had a history of depression at baseline (age of onset at or before CDAH-1), to examine incident depression. Statistical analyses were conducted with STATA software (version 12.0, 2011, Statacorp, College Station, Texas).

**RESULTS**

In total, 544 men and 925 women completed the food frequency questionnaire at baseline and the CIDI at follow-up. The different participation rates for men and women are due to a lower proportion of men responding to the postal questionnaire in CDAH-2 (37% men). Participants who were missing covariates included in the adjusted models (11 men, 71 women) and one woman with an implausibly high fish intake (107.5 times/week) were excluded, leaving 533 men and 853 women for the analysis. **Table 1** shows the participants baseline characteristics.

Compared to the Australian population of 25-34 year olds, a higher percentage of the CDAH sample at baseline was married or living as married (57% of men, 64% of women in the Australian population (37)) and employed as professionals or managers (40% of men, 38% of women in the general population (38)). The percentage classified as being overweight or

obese (BMI ≥25kg/$m^2$) was similar to that of the general population of the same age (58% of men, 35% of women (39)).

Mean follow-up time was 4.96(0.34) years. During follow-up, 70(13.1%) men and 160(18.8%) women had a depressive episode. The prevalence of lifetime depression (ever having depression/dysthymia) was higher in the CDAH sample than in the general Australian population of 31-41 year old men (18.1% vs 13.5%, respectively) and women (29.4% vs 21.8%, respectively). Participation in CDAH-2 was not affected by depression status in CDAH-1 (78.2% for those who had 12 month depression at CDAH-1 and 78.6% for those who did not).

Median fish consumption at baseline was the same for men and women at 2 (interquartile range:1,4) times/week. Fish was consumed ≥2 times/week by 320(60.0%) men and 506(59.3%) women. The most common sources of fish were canned fish (median:0.5, interquartile range:0, 1 times/week for men and women) and fresh fish (median:0.5, interquartile range:0, 0.5 times/week for men and women). Fish oil or evening primrose oil supplements were used at least once per month at baseline by 37(6.9%) men and 119(14.0%) women (Table 1). Very few participants usually used omega-3 margarine for cooking (10 men, 11 women) or as a spread (13 men, 25 women).

For women, baseline factors associated with having depression during the follow-up period were marital status (being single), smoking status (being a current smoker), being overweight or obese and poorer self-rated health (**Web Table 1**). For men, use of fish oil/evening primrose oil supplements was the only baseline characteristic associated with depression, with supplement use being higher in depressed men. These factors were included as covariates in the analyses.

For women, after adjusting for marital status, smoking status, weight status and self-rated health, there was a trend for each additional serve of fish per week at baseline to reduce the risk of having depression during follow-up by 6%. Women who ate fish ≥2 times/week at baseline had a 25% lower risk of having depression during follow-up, than those who ate fish <2 times/week (**Table 2**). For men, baseline fish consumption was not associated with the risk of depression.

Reverse causation was also suggested with women who had an episode of depression since baseline being 15% less likely to eat fish ≥2 times/week at follow-up compared to women who had not had depression, after adjusting for marital status, smoking status, weight status and self-rated health (adjusted relative risk:0.85, 95% confidence interval:0.71,1.00). When those who had depression in the 12 months prior to follow-up, i.e. those whose symptoms were most recent, were excluded from the analysis the association disappeared (adjusted relative risk:0.98, 95% confidence interval:0.81,1.19). For men, depression was not associated with fish intake at follow-up (adjusted relative risk:1.12, 95% confidence interval:0.91,1.38, adjusted for fish oil/evening primrose oil supplementation).

*Sensitivity analyses* (see **Web Appendix**)*:* Similar results were observed when fish intake at baseline and follow-up was averaged. When individuals who had a history of depression at baseline were excluded, the magnitude of the association remained the same but was no longer statistically significant, probably due to the smaller sample size (**Web Table 2**). For consistency, we repeated the analysis for men using the same model used for women, which did not significantly change the results (**Web Table 3**). Additional adjustments for use of fish oil/evening primrose oil or antidepressant medication, or replacing weight status with BMI did not change the results for women.

**DISCUSSION**

In this longitudinal study of Australian adults, higher fish consumption was associated with a significantly lower risk of having a depressive episode in women, but not men, during approximately 5 years follow-up. While there was also a suggestion of reverse causation, this appeared to be restricted to those who had depression relatively recently and their lower fish intake at follow-up may have been a result of disturbed eating patterns associated with depressive symptoms. To our knowledge, this is the first study to examine longitudinal associations between fish consumption and depression using a diagnostic tool to define depression.

Our findings are consistent with previous cross-sectional studies that have shown a lower risk of depression in healthy adults with higher fish consumption (6,9-11). Similar sex-specific findings were reported in two cross-sectional studies conducted in Finland that reported depression, measured using a screening tool or self-reported doctor diagnosis, was significantly lower in women who ate fish ≥1/week (7,8). Both studies reported no significant associations between fish consumption and depression in men. In the CARDIA study, baseline fish consumption was not associated with depressive symptoms at the 3-year follow-up. However, at the 13-year follow-up, there was a dose response relationship between baseline fish consumption and chronicity of depression, with women who had higher fish consumption having depressive symptoms at fewer of the three follow-up visits (40). The observed protective association for women but not men may be due to men consuming more omega-3 fatty acids from other dietary sources, particularly from meat. Fish is the best source of omega-3 fatty acids but in Australia, pasture fed meat, poultry and game contribute similar amounts of omega-3 to the diet because they are consumed about

six times more than fish and seafood (41). Alternatively, interactions between sex hormones and omega-3 fatty acids might provide another explanation. A study examining the association between omega-3 fatty acids and platelet aggregation, found men benefited more from eicosapentaenoic acid supplementation while females responded better to docosahexaenoic acid (42). The results may also be explained by differential reporting of fish intake between men and women, leading to exposure misclassification, or different types of fish consumed by men and women, which would not be detected in the food frequency questionnaire.

In contrast to our findings, several studies have reported beneficial associations only in men. Higher fish consumption was associated with lower depression in men but not women in two Finnish cross-sectional studies (13). In a large national sample in the USA, men who ate fish ≥2 times/week at baseline were significantly less likely to have severely depressed mood at the 10-year follow-up than those eating fish ≤1 time/week (17). The reasons for these sex differences are not clear but may reflect the different sampling of the study populations or methods used to determine fish intake and depression, the large age range or older adult samples, or possibly residual confounding.

The biological mechanism linking fish consumption and depression is not well understood but it has been postulated that omega-3 fatty acids may alter the phospholipid composition of cell membranes or cause changes to the membrane microstructure and the function of membrane-associated proteins (17). Although omega-3 fatty acids are hypothesised to be the beneficial component of fish, the results from randomised controlled trials examining the association between omega-3 supplements and depressive symptoms have been inconclusive (20). The associations between fish consumption and depression might be due

to confounding by healthier diet and lifestyle and better psychosocial circumstances (10). In our adjusted models, when we included marital status, smoking status, weight status and health status the results were only slightly attenuated and remained statistically significant. Other lifestyle factors considered to be important in previous studies, such as physical activity, other dietary components and alcohol consumption, were not associated with depression in this sample and therefore could not be confounders. However, residual confounding by lifestyle or socio-economic factors not measured in this study is possible.

Fish consumption was fairly high, with about 60% of men and women consuming fish ≥2 times/week. Canned and fresh fish were the most common sources. Canned fish is a relatively cheap option in Australia but fresh fish is expensive unless self-caught. The CDAH sample is of higher socioeconomic status than the general Australian population, which may mean participants could afford to frequently eat fish. There is no recent published national data on fish consumption in Australia but a population health survey of ~3,500 18-75 year olds conducted in 2009-10 in Victoria, the second most populated state in Australia, reported a mean intake of fish and seafood of 38.3g/day for men and 32.3g/day for women. When converted to serves/week (one serve=120g (43)), on average, men were eating 2.2 serves/week and women 1.9 serves/week. Fish consumption may be higher in the CDAH sample due to different socioeconomic status, age ranges and methods used to assess fish consumption between the studies. Alternatively fish consumption may have been overestimated due to the large number of items (nine) included in this variable. However, an Australian study found an aggregate measure of 71 fish items was a valid measure of fish consumption when compared with erythrocyte membrane eicosapentaenoic acid (44).

Several limitations need to be taken into consideration when interpreting these results. The prevalence of lifetime depression was higher in the CDAH study sample than in participants of similar age in the 2007 Australian National Survey of Mental Health and Wellbeing, the most recent national survey. However, the National Survey used the CIDI 3.0, which has a different structure and includes some different questions in the depression section. Therefore the prevalence derived from the two different versions of the CIDI may not be directly comparable. Consistent with the national data, the prevalence of depression was higher in women than men in the CDAH study. The CIDI does not give timing of every episode of depression therefore we were unable to examine associations of fish consumption with individual episode occurrence. Participation in CDAH-2 was not affected by depression status in CDAH-1.

The questionnaire did not differentiate between fatty and lean fish, which is a limitation as the omega-3 concentration is much higher in fatty fish. However, this would result in underestimating the effect estimate, as consumption of only fatty fish may have an even stronger association on reducing the risk of depression. Information on portion size was not collected and therefore it is not known how many serves of fish participants were actually consuming at each eating occasion. The use of fish oil supplements may be overestimated, as fish oil and evening primrose oil supplements were combined in the questionnaire and this may underestimate the true effect estimate. Energy intake was not available. However, the analysis was stratified by sex and other key determinants of energy intake (age and physical activity) were not associated with fish consumption.

The environmental impact of recommending increased intake of fish for mental and physical health needs to be considered. Concerns have been raised regarding the potential over-

fishing of wild fish stocks and using wild fish to feed farmed fish (45). It is important to identify sustainable sources of fish to ensure long term viability and affordability. In the CDAH study, use of fish oil supplements and omega-3 fortified foods was low. Eating fish rather than taking supplements can provide benefits other than omega-3 fatty acids, as fish is a good source of high quality protein, vitamins and minerals.

In summary, this study is an advance on previous work in this area by using the “gold standard” diagnostic tool (the CIDI), rather than a screening tool or self-report, to define depression. Findings from this longitudinal study suggest that, for women, fish consumption may be protective against depression. Depression was also associated with lower intake of fish around the time of the depressive episode. Data was available for a wide range of potential confounders. The findings add to the growing evidence that fish consumption may be beneficial for women’s mental health.

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**Figure 1. Flow Chart Illustrating the Childhood Determinants of Adult Health Study Participants Included in The Analysis, Australia 1985-2011.**

Participants who were initially non-responders were given the option of completing a shorter protocol by telephone interview, which included shorter versions of the questionnaires (no food frequency questionnaire) at CDAH-1 and CDAH-2 and excluded the CIDI at CDAH-2.

Participants were excluded from the analysis if they did not answer all of the fish items in the food frequency questionnaire at baseline.

Abbreviations: CDAH, Childhood Determinants of Adult Health study; CIDI, Composite International Diagnostic Interview.

**Table 1. Baseline Socio-demographic and Anthropometric Characteristics of the Childhood Determinants of Adult Health Study Participants, Australia, 2004-06**

| Socio-demographic/anthropometric characteristic | Men (N=533)[a] | | Women (N=853)[a] | |
|---|---|---|---|---|
| | n | % | n | % |
| Age [b] | 31.8 (2.6) | | 31.5 (2.6) | |
| Married or living as married | 362 | 67.9 | 637 | 74.7 |
| Education | | | | |
| University | 232 | 43.6 | 445 | 52.2 |
| Vocational | 180 | 33.8 | 193 | 22.6 |
| School only | 120 | 22.6 | 215 | 25.2 |
| Occupation | | | | |
| Professional or manager | 328 | 62.4 | 446 | 53.0 |
| Non-manual | 40 | 7.6 | 203 | 24.1 |
| Manual | 137 | 26.0 | 30 | 3.6 |
| Not in the workforce | 21 | 4.0 | 163 | 19.4 |
| BMI | | | | |
| Normal (<25kg/$m^2$) | 238 | 47.2 | 545 | 63.9 |
| Overweight (25-29.9kg/$m^2$) | 199 | 39.5 | 204 | 23.9 |
| Obese (≥30kg/$m^2$) | 67 | 13.3 | 104 | 12.2 |

Abbreviations: BMI, body mass index.

[a] Sample sizes vary due to missing data (range 479 to 504 for men; 753 to 764 for women).

[b] Mean (SD)

**Table 2. Relative Risk for Having a New Episode of Depression Since Baseline, by Fish Consumption, the Childhood Determinants of Adult Health Study, Australia, 2004-2011**

| | Depression | | | Unadjusted | | | Adjusted[a] | | |
|---|---|---|---|---|---|---|---|---|---|
| Fish consumption | n | Total No. | % | RR | 95% CI | P-value[b] | RR | 95% CI | P-Value[b] |
| **Women** (N=853) | | | | | | | | | |
| Times/week | 160 | 853 | 18.8 | 0.93 | 0.86, 1.01 | *P*=0.07 | 0.94 | 0.87, 1.01 | *P*=0.07 |
| <2 times/week | 79 | 347 | 22.8 | 1.00 | REF | | 1.00 | REF | |
| ≥2 times/week | 81 | 506 | 16.0 | 0.70 | 0.53, 0.93 | *P*=0.01 | 0.75 | 0.57, 0.99 | *P*=0.04 |
| **Men** (N=533) | | | | | | | | | |
| Times/week | 70 | 533 | 13.9 | 1.03 | 0.96, 1.11 | *P*=0.38 | 1.02 | 0.95, 1.10 | *P*=0.54 |
| <2 times/week | 25 | 213 | 11.7 | 1.00 | REF | | 1.00 | REF | |
| ≥2 times/week | 45 | 320 | 14.1 | 1.20 | 0.76, 1.89 | *P*=0.44 | 1.17 | 0.74, 1.86 | *P*=0.49 |

Abbreviations: RR, relative risk; CI, confidence interval.

[a]Analyses for women adjusted for baseline marital status, smoking status, weight status and self-reported health. Analyses for men adjusted for the use of fish oil/evening primrose oil supplements.

[b] P-values calculated using Poisson regression with robust standard errors.