# Supplemental Online Content

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**eReferences.**

This supplemental material has been provided by the authors to give readers additional information about their work.

**eTable 1.** Detailed Baseline Characteristics of Participants, According to Randomized Omega-3 Fatty Acid and Placebo Groups.

| Baseline Characteristic | Omega-3 group (n=9171)[a] | Placebo group (n=9182)[a] |
|---|---|---|
| Age, y, mean (SD) | 67.4 (7.1) | 67.5 (7.0) |
| Age groups, y, no. (%) | | |
| 50-54 | 354 (3.9) | 298 (3.3) |
| 55-64 | 2947 (32.1) | 3018 (32.9) |
| 65-74 | 4633 (50.5) | 4598 (50.1) |
| 75+ | 1237 (13.5) | 1268 (13.8) |
| Sex, no. (%) | | |
| Males | 4674 (51.0) | 4656 (50.7) |
| Females | 4497 (49.0) | 4526 (49.3) |
| Racial or ethnic group, no. (%)[b] | n=8982 | n=9007 |
| African American/Black | 1683 (18.7) | 1724 (19.1) |
| Asian/Pacific Islander | 150 (1.7) | 144 (1.6) |

| **Baseline Characteristic** | **Omega-3 group (n=9171)[a]** | **Placebo group (n=9182)[a]** |
|---|---|---|
| Hispanic (not African American) | 347 (3.9) | 361 (4.0) |
| Native American/Alaskan Native | 80 (0.9) | 70 (0.8) |
| Non-Hispanic White | 6563 (73.1) | 6534 (72.5) |
| Other[c] | 159 (1.8) | 174 (1.9) |
| Greater than high school education, no./total no. (%) | 8043 / 9153 (87.9) | 8122 / 9162 (88.7) |
| Income $30,000+ per year, no./total no. (%) | 6932 / 8248 (84.0) | 6853 / 8232 (83.3) |
| Body-mass index[d], mean (SD) [N] | 27.8 (5.5) [8950] | 27.7 (5.5) [8969] |
| Hypertension treated with medication, no./total no. (%) | 4560 / 9126 (50.0) | 4638 / 9136 (50.8) |
| Current use of cholesterol-lowering medication, no./total no. (%) | 3322 / 9123 (36.4) | 3302 / 9150 (36.1) |
| Diabetes, no./total no. (%) | 1165 / 9158 (12.7) | 1143 / 9167 (12.5) |
| Smoking, no. (%) | n=9124 | n=9143 |
| Current | 4882 (53.5) | 4856 (53.1) |
| Past | 3684 (40.4) | 3724 (40.7) |
| Never | 558 (6.1) | 563 (6.2) |

| **Baseline Characteristic** | **Omega-3 group (n=9171)[a]** | **Placebo group (n=9182)[a]** |
|---|---|---|
| Alcohol use frequency, no. (%) | n=9047 | n=9045 |
| Never/rarely | 2716 (30.0) | 2758 (30.5) |
| Monthly | 678 (7.5) | 641 (7.1) |
| Weekly | 3242 (35.8) | 3218 (35.6) |
| Daily | 2411 (26.7) | 2428 (26.8) |
| Total physical activity, MET-hours/week, median (IQR), [N] | 16.8 (5.6-32.9) [9168] | 17.0 (5.5-33.4) [9182] |
| Current postmenopausal hormone use (females only), no./total no. (%)[e] | 462 / 4416 (10.5) | 477 / 4454 (10.7) |
| Current use of multivitamins, no./total no. (%) | 4072 / 9044 (45.0) | 4101 / 9040 (45.4) |
| Current use of supplemental vitamin D, no./total no. (%)[f] | 4067 / 9171 (44.4) | 4063 / 9182 (44.3) |
| Current use of supplemental calcium (≤1200 mg/day), no./total no. (%)[g] | 1848 / 9171 (20.2) | 1905 / 9182 (20.8) |
| Intake of foods related to vitamin D and/or omega-3 fatty acids,[h] mean (SD) [N] | | |

| **Baseline Characteristic** | **Omega-3 group (n=9171)[a]** | **Placebo group (n=9182)[a]** |
|---|---|---|
| Milk, servings/day[i] | 0.7 (0.9) [8967] | 0.7 (0.9) [8960] |
| Other vitamin D-fortified foods, servings/day[j] | 0.6 (0.7) [9035] | 0.6 (0.7) [9042] |
| Dark-meat fish, servings/week[k] | 1.0 (1.7) [9023] | 1.0 (1.4) [9030] |
| Other fish and seafood, servings/week[l] | 1.1 (1.7) [9031] | 1.1 (1.8) [9033] |
| Baseline biomarker levels, median (IQR) [N] | | |
| 25-(OH)D, ng/ml[m] | 31.0 (25.0-37.0) [5708] | 31.0 (25.0-37.0) [5709] |
| EPA, %[n] | 0.5 (0.4-0.7) [5591] | 0.5 (0.4-0.7) [5638] |
| DHA, %[n] | 1.9 (1.5-2.4) [5598] | 1.9 (1.6-2.4) [5639] |
| Geographic region, no. (%) | n=9170 | n=9182 |
| Southeast | 2483 (27.1) | 2548 (27.8) |
| Northeast | 2511 (27.4) | 2492 (27.1) |
| West | 2172 (23.7) | 2116 (23.1) |
| Midwest | 2004 (21.9) | 2026 (22.1) |
| Charlson-Deyo comorbidity index,[n] no. (%) | | |

| Baseline Characteristic | Omega-3 group (n=9171)[a] | Placebo group (n=9182)[a] |
|---|---|---|
| 0 point | 7764 (84.7) | 7776 (84.7) |
| 1 point | 1206 (13.2) | 1199 (13.1) |
| 2+ points | 201 (2.2) | 207 (2.3) |
| Randomization in Vitamin D3 portion of trial, no. (%) | | |
| Active agent group | 4608 (50.3) | 4573 (49.8) |
| Placebo group | 4563 (49.8) | 4609 (50.2) |

Abbreviations: SD, standard deviation; IQR, interquartile range; MET, metabolic equivalent of task; 25(OH)D, 25-hydroxyvitamin D; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid

[a] Unless otherwise stated.

[b] Racial and ethnic group were reported by participants.

[c] Other race/ethnicity includes Native Hawaiian or other Pacific Islander, multiple race or unknown race or unknown ethnicity.

[d] Body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for 2.4% of the participants.

[e] Virtually all female participants are postmenopausal (>99%).

[f] ≤800 IU/day from all supplemental sources of vitamin D combined (individual vitamin D supplements, calcium + vitamin D supplements, medications with vitamin D [e.g., Fosamax Plus D], and multivitamins)

[g] ≤1200 mg/day from all supplemental sources of calcium combined

[h] As assessed by a modified version of the Harvard Food Frequency Questionnaire.

[i] Milk: Dairy and soy-milk

[j] Other vitamin-D fortified foods: vitamin D-fortified cereal, vitamin D-fortified orange juice, yogurt

[k] Dark-meat fish: e.g., mackerel, salmon, sardines, bluefish, swordfish, canned tuna

[l] Other fish and seafood: e.g., cod, haddock, halibut, breaded fish cakes, pieces, or fish sticks, shrimp, lobster, scallops

[m] To convert 25(OH)D units to a nanomoles per liter, multiply by 2.5.

[n] Baseline plasma levels of EPA and DHA were expressed as a percent of total phospholipid fatty acids.

[o] The Charlson-Deyo comorbidity index is a weighted comorbidity score derived from the sum of the scores for each of several major medical comorbid conditions[1,2]. Participants were categorized as having 0, 1, or ≥2 points on the Charlson-Deyo comorbidity index.

**eTable 2.** Mean Difference in Change Since Baseline in PHQ-8 Score Comparing Omega-3 Fatty Acid and Placebo Groups, According to Baseline Sub-groups.[a]

| Group | No. of participants | Mean difference (95% CI) | P-value (P-interaction)[b] |
|---|---|---|---|
| Sex | | | 0.16 |
| Female | 9,023 | 0.06 (-0.00, 0.12) | |
| Male | 9,330 | -0.00 (-0.06, 0.06) | |
| Age (years) | | | 0.34 |
| 50-64 | 6,617 | -0.00 (-0.08, 0.07) | |
| 65-74 | 9,231 | 0.04 (-0.02, 0.09) | |
| 75+ | 2,505 | 0.10 (-0.01, 0.22) | |
| Racial or ethnic group[c] | | | 0.93 |
| African American/Black | 3407 | 0.05 (-0.08, 0.18) | |
| Non-Hispanic White | 13097 | 0.03 (-0.02, 0.08) | |
| Other[d] | 1485 | 0.02 (-0.15, 0.19) | |
| Baseline plasma EPA level, %[e] | | | 0.70 |

| Group | No. of participants | Mean difference (95% CI) | P-value (P-interaction)[b] |
|---|---|---|---|
| < Median of 0.50 | 4318 | 0.03 (-0.05, 0.12) | |
| ≥ Median of 0.50 | 6911 | 0.06 (-0.01, 0.12) | |
| Baseline plasma DHA level, %[e] | | | 0.87 |
| < Median of 1.90 | 5001 | 0.05 (-0.03, 0.13) | |
| ≥ Median of 1.90 | 6236 | 0.04 (-0.03, 0.11) | |
| Total fish & seafood intake[f] | | | 0.20 |
| < Median of 1.47 servings/week | 9555 | 0.01 (-0.05, 0.07) | |
| ≥ Median of 1.47 servings/week | 8523 | 0.06 (0.00, 0.13) | |
| Charlson-Deyo comorbidity index[g] | | | 0.29 |
| 0 point | 15540 | 0.01 (-0.03, 0.06) | |
| 1 point | 2405 | 0.07 (-0.07, 0.22) | |
| 2+ points | 408 | 0.30 (-0.07, 0.68) | |
| Randomization in Vitamin D3 portion of trial | | | 0.24 |

| Group | No. of participants | Mean difference (95% CI) | P-value (P-interaction)[b] |
|---|---|---|---|
| Active agent group | 9181 | 0.00 (-0.06, 0.06) | |
| Placebo group | 9172 | 0.05 (-0.01, 0.12) | |

Abbreviation: CI, confidence interval; PHQ, patient health questionnaire; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid

[a] Analyses were from general linear models of response profiles to estimate the means, with time modeled as indicator variables; models were controlled for age, sex, and vitamin D3 randomization group. Adjusted mean differences (95% CI) between the omega-3 fatty acid and placebo groups in PHQ-8 change scores averaged across all follow-up years (years 1-5) are shown within sub-groups.

[b] P-interaction is from the test of the sub-group-x-treatment-x-follow-up time interaction term in the model.

[c] Racial and ethnic group were reported by participants.

[d] Other race/ethnicity group included Hispanic (not African American), Asian, Native Hawaiian or other Pacific Islander, multiple race or unknown race or unknown ethnicity.

[e] Baseline plasma levels of EPA and DHA were expressed as a percent of total phospholipid fatty acids.

[f] Total fish and seafood intake includes dark-meat fish: e.g., mackerel, salmon, sardines, bluefish, swordfish; canned tuna, Other fish and seafood: e.g., cod, haddock, halibut; breaded fish cakes, pieces, or fish sticks; shrimp, lobster, scallops.

[g] The Charlson-Deyo comorbidity index is a weighted comorbidity score derived from the sum of the scores for each of several major medical comorbid conditions[1,2]. Participants were categorized as having 0, 1, or ≥2 points on the Charlson-Deyo comorbidity index.

**eTable 3.** Adjusted Means at Baseline and Mean Change (95% CI) in PHQ-8 Scores at Each Year Since Randomization Compared to Baseline, According to Omega-3 Fatty Acid and Placebo Groups, Censoring PHQ-8 Scores after Initiation of Antidepressants.[a]

| PHQ-8 score | Omega-3 group | | Placebo group | | Mean difference (95% CI)[b] | P-value | P-interaction |
|---|---|---|---|---|---|---|---|
| | Number of participants | Adjusted mean (95% CI) | Number of participants | Adjusted mean (95% CI) | | | |
| Baseline | 9171 | 1.09 (1.06, 1.13) | 9182 | 1.11 (1.08, 1.15) | -- | -- | 0.51 |
| Year 1 vs Baseline | 8411 | 0.04 (0.00, 0.07) | 8506 | 0.01 (-0.03, 0.04) | 0.03 (-0.02, 0.08) | 0.28 | |
| Year 2 vs Baseline | 8245 | 0.06 (0.02, 0.10) | 8297 | 0.03 (-0.01, 0.07) | 0.03 (-0.03, 0.08) | 0.37 | |
| Year 3 vs Baseline | 7973 | 0.09 (0.05, 0.13) | 8052 | 0.05 (0.01, 0.09) | 0.05 (-0.01, 0.11) | 0.11 | |
| Year 4 vs Baseline | 7500 | 0.06 (0.02, 0.10) | 7545 | 0.04 (0.00, 0.08) | 0.02 (-0.04, 0.08) | 0.43 | |
| Year 5 vs Baseline | 5144 | 0.15 (0.10, 0.20) | 5133 | 0.17 (0.12, 0.22) | -0.01 (-0.08, 0.06) | 0.70 | |
| **Average (across Years 1-5) vs Baseline** | **9171** | | **9182** | | **0.03 (-0.02, 0.07)** | 0.24 | |

Abbreviation: CI, confidence interval; PHQ, patient health questionnaire

[a] Analyses were from general linear models of response profiles to estimate the means, with time modeled as indicator variables; models were controlled for age, sex, and vitamin D3 randomization group. Adjusted means (95% CI) within each treatment group are shown at baseline and adjusted mean differences in change (95% CI) within each treatment group are shown for each follow-up time point. P-interaction is from the 5-degree-freedom test of the treatment-x-time interaction term in the model.

[b] Mean differences in change comparing omega-3 fatty acid and placebo groups; the last row shows the adjusted mean difference (95% CI) between the omega-3 fatty acid and placebo groups in PHQ-8 change scores averaged across all follow-up years (years 1-5 vs. baseline).

**eTable 4.** Participant-Reported Adherence with the Omega-3 Fatty Acid and Placebo Study Pills (% of Pills Taken) for All Time Points, among Participants Responding to Compliance Questionnaires.

| Time | Omega-3 group | Placebo group |
|---|---|---|
| Baseline | 9171/9171 (100.0) | 9182/9182 (100.0) |
| Year 1 | 8162/8634 (94.5) | 8228/8683 (94.8) |
| Year 2 | 7743/8417 (92.0) | 7759/8393 (92.5) |
| Year 3 | 7441/8156 (91.2) | 7436/8148 (91.3) |
| Year 4 | 7031/7707 (91.2) | 7013/7689 (91.2) |
| Year 5 | 4650/5149 (90.3) | 4632/5086 (91.1) |

**eTable 5.** Hazard Ratios and 95% CIs for Total, Incident and Recurrent Depression, According to Randomized Assignment to Omega-3 Fatty Acid or Placebo, with Additional Censoring at Time Taking Less than 2/3 Study Pills.[a]

| Outcome | Omega-3 group | Placebo group | HR (95% CI) | P-value |
|---|---|---|---|---|
| | *Event/no. of participants* | | | |
| Total depression[b] | 516/9171 | 454/9182 | 1.15 (1.01 – 1.30) | 0.03 |
| Incident depression[c] | 385/8322 | 340/8355 | 1.14 (0.99 – 1.32) | 0.08 |
| Recurrent depression[c] | 131/849 | 114/847 | 1.14 (0.89 – 1.47) | 0.31 |

Abbreviation: HR, hazard ratio; CI, confidence interval

[a] Analyses were from Cox regression models that were controlled for age, sex, and vitamin D3 randomization group. Analyses were not adjusted for multiple comparisons.

[b] Depression is a composite outcome comprising reported presence of clinician diagnosis of depression, treatment for depression and/or symptoms above the validated cutoff for major depression on the PHQ-8(PHQ-8≥10); total depression consists of all incident and recurrent depression combined.

[c] Incident and recurrent depression were exploratory outcomes. Incident depression was defined as depression cases that occurred among those with no past history of depression; recurrent depression was defined as depression cases that occurred among those with past history of depression, but not under treatment or active in the past 2 years.

**eTable 6a.** Hazard Ratios and 95% CIs for Total, Incident, and Recurrent Depression, According to Randomized Assignment to Omega-3 Fatty Acid or Placebo, with Additional Censoring at Incident CVD.[a]

| Outcome | Omega-3 group | Placebo group | HR (95% CI) | P-value |
|---|---|---|---|---|
| | *Event/no. of participants* | | | |
| Total depression[b] | 638/9171 | 566/9182 | 1.14 (1.02 – 1.28) | 0.02 |
| Incident depression[c] | 483/8322 | 416/8335 | 1.17 (1.03 – 1.34) | 0.02 |
| Recurrent depression[c] | 155/849 | 150/847 | 1.04 (0.83 – 1.30) | 0.76 |

Abbreviation: HR, hazard ratio; CI, confidence interval

[a] Analyses were from Cox regression models that were controlled for age, sex, and vitamin D3 randomization group. Analyses were not adjusted for multiple comparisons.

[b] Depression is a composite outcome comprising reported presence of clinician diagnosis of depression, treatment for depression and/or symptoms above the validated cutoff for major depression on the PHQ-8(PHQ-8≥10); total depression consists of all incident and recurrent depression combined.

[c] Incident and recurrent depression were exploratory outcomes. Incident depression was defined as depression cases that occurred among those with no past history of depression; recurrent depression was defined as depression cases that occurred among those with past history of depression, but not under treatment or active in the past 2 years.

**eTable 6b.** Hazard Ratios and 95% CIs for Total, Incident, and Recurrent Depression, According to Randomized Assignment to Omega-3 Fatty Acid or Placebo, with Additional Adjustment for CVD as a Time-Dependent Covariate.[a]

| Outcome | Omega-3 group | Placebo group | HR (95% CI) | P-value |
|---|---|---|---|---|
| | *Event/no. of participants* | | | |
| Total depression[b] | 651/9171 | 583/9182 | 1.13 (1.01 – 1.26) | 0.03 |
| Incident depression[c] | 493/8322 | 427/8335 | 1.17 (1.03 – 1.33) | 0.02 |
| Recurrent depression[c] | 158/849 | 156/847 | 1.02 (0.82 – 1.27) | 0.87 |

Abbreviation: HR, hazard ratio; CI, confidence interval

[a] Analyses were from Cox regression models that were controlled for age, sex, time-dependent CVD variable and vitamin D3 randomization group. Analyses were not adjusted for multiple comparisons.

[b] Depression is a composite outcome comprising reported presence of clinician diagnosis of depression, treatment for depression and/or symptoms above the validated cutoff for major depression on the PHQ-8(PHQ-8≥10); total depression consists of all incident and recurrent depression combined.

[c] Incident and recurrent depression were exploratory outcomes. Incident depression was defined as depression cases that occurred among those with no past history of depression; recurrent depression was defined as depression cases that occurred among those with past history of depression, but not under treatment or active in the past 2 years.

**eTable 7a.** Hazard Ratios and 95% CIs for Total, Incident, and Recurrent Depression, According to Randomized Assignment to Omega-3 Fatty Acid or Placebo, with Additional Censoring at Incident Cancer.[a]

| Outcome | Omega-3 group | Placebo group | HR (95% CI) | P-value |
|---|---|---|---|---|
| | *Event/no. of participants* | | | |
| Total depression[b] | 629/9171 | 563/9182 | 1.13 (1.01 – 1.27) | 0.04 |
| Incident depression[c] | 474/8322 | 412/8335 | 1.16 (1.02 – 1.33) | 0.03 |
| Recurrent depression[c] | 155/849 | 151/847 | 1.04 (0.83 – 1.30) | 0.75 |

Abbreviation: HR, hazard ratio; CI, confidence interval

[a] Analyses were from Cox regression models that were controlled for age, sex, and vitamin D3 randomization group. Analyses were not adjusted for multiple comparisons.

[b] Depression is a composite outcome comprising reported presence of clinician diagnosis of depression, treatment for depression and/or symptoms above the validated cutoff for major depression on the PHQ-8(PHQ-8≥10); total depression consists of all incident and recurrent depression combined.

[c] Incident and recurrent depression were exploratory outcomes. Incident depression was defined as depression cases that occurred among those with no past history of depression; recurrent depression was defined as depression cases that occurred among those with past history of depression, but not under treatment or active in the past 2 years.

**eTable 7b.** Hazard Ratios and 95% CIs for Total, Incident, and Recurrent Depression, According to Randomized Assignment to Omega-3 Fatty Acid or Placebo, with Additional Adjustment for Total Cancer as a Time-Dependent Covariate.[a]

| Outcome | Omega-3 group | Placebo group | HR (95% CI) | P-value |
|---|---|---|---|---|
| | *no. of participants with event* | | | |
| Total depression[b] | 651/9171 | 583/9182 | 1.13 (1.01 – 1.26) | 0.03 |
| Incident depression[c] | 493/8322 | 427/8335 | 1.17 (1.03 – 1.33) | 0.02 |
| Recurrent depression[c] | 158/849 | 156/847 | 1.02 (0.81 – 1.27) | 0.88 |

Abbreviation: HR, hazard ratio; CI, confidence interval

[a] Analyses were from Cox regression models that were controlled for age, sex, time-dependent malignant cancer and vitamin D3 randomization group. Analyses were not adjusted for multiple comparisons.

[b] Depression is a composite outcome comprising reported presence of clinician diagnosis of depression, treatment for depression and/or symptoms above the validated cutoff for major depression on the PHQ-8(PHQ-8≥10); total depression consists of all incident and recurrent depression combined.

[c] Incident and recurrent depression were exploratory outcomes. Incident depression was defined as depression cases that occurred among those with no past history of depression; recurrent depression was defined as depression cases that occurred among those with past history of depression, but not under treatment or active in the past 2 years.

**Description of Results from Sensitivity Analyses in eTable 6 and eTable 7.**

There were no differences in results with additional censoring at developing of parent trial CVD outcomes (total depression HR, 95% CI: 1.14, 1.02-1.28). While development of CVD was strongly associated with 3-fold risk of total depression (HR, 95% CI: 2.96, 2.05-4.27), incident depression (HR, 95% CI: 2.72, 1.76-4.21) and recurrent depression (HR, 95% CI: 2.85, 1.46-5.55), and omega-3 was associated with reduced risk of several secondary CVD outcomes in the parent trial[3], there were no differences in results for the effect of omega-3 on depression risk when including CVD as a time-updated covariate (total depression HR, 95% CI: 1.13, 1.01-1.26). Development of cancer was not statistically significantly associated with total (HR, 95% CI: 1.21, 0.89-1.65), incident (HR, 95% CI: 1.28, 0.91-1.81) or recurrent depression (HR, 95% CI: 0.97, 0.48-1.97). As with CVD outcomes, there were no differences in results when censoring or adjusting for time-updated parent trial cancer outcomes.

**eTable 8.** Subdistribution Hazard Models Comparing the Risk of Depression in the Omega-3 Fatty Acid and Placebo Groups.[a]

| Outcome | No. of participants | HR (95% CI) | P-value |
|---|---|---|---|
| Total depression[b] | 18,353 | 1.13 (1.01-1.26) | 0.03 |
| Incident depression[c] | 16,657 | 1.17 (1.02-1.33) | 0.02 |
| Recurrent depression[c] | 1696 | 1.01 (0.81-1.26) | 0.91 |

Abbreviation: HR, hazard ratio; CI, confidence interval

[a] The adjusted HRs were computed from the Fine and Gray subdistribution hazard models. Analyses used the Fine-Gray competing risks approach; death from any cause was treated as a competing rather than censored event. Results from the subdistribution hazard models are shown for total, incident and recurrent depression or clinically relevant depressive symptoms.

[b] Depression is a composite outcome comprising reported presence of clinician diagnosis of depression, treatment for depression and/or symptoms above the validated cutoff for major depression on the PHQ-8 (PHQ-8≥10); total depression consists of all incident and recurrent depression combined.

[c] Incident and recurrent depression were exploratory outcomes. Incident depression was defined as depression cases that occurred among those with no past history of depression; recurrent depression was defined as depression cases that occurred among those with past history of depression, but not under treatment or active in the past 2 years.

**eTable 9.** Adjusted Differences in Change in PHQ-8 Scores Since Baseline, Comparing Omega-3 Fatty Acid to Placebo.[a]

| Effect | Omega-3 group, N | Placebo group, N | Rate ratio (95% CI) | P-Value |
|---|---|---|---|---|
| Year 1 vs Baseline | 8471 | 8549 | 1.03 (0.98-1.08) | 0.27 |
| Year 2 vs Baseline | 8354 | 8371 | 1.02 (0.97-1.07) | 0.44 |
| Year 3 vs Baseline | 8116 | 8172 | 1.04 (0.99-1.09) | 0.16 |
| Year 4 vs Baseline | 7676 | 7690 | 1.03 (0.98-1.08) | 0.28 |
| Year 5 vs Baseline | 5295 | 5252 | 0.99 (0.94-1.04) | 0.83 |
| **Average over Years 1-5 vs Baseline** | **9171** | **9182** | **1.02 (0.98-1.06)** | **0.23** |

Abbreviation: CI, confidence interval; PHQ, patient health questionnaire

[a] Analyses were from repeated measures negative binomial regression models, with follow-up time modeled as an indicator; models were controlled for age, sex, and vitamin D3 randomization group. Results show rate ratios (RRs) and 95% confidence intervals (95% CIs), which reflect percent differences in the change in severity on the PHQ-8 score comparing omega-3 fatty acid to placebo treatment group. RRs are shown for each follow-up time point, and for the average over all follow-up. Results show no significant differences between the treatment groups in change in PHQ-8 scores since baseline.

**eTable 10.** Adjusted Means at Baseline and Mean Change (95% CI) in PHQ-8 Scores at Each Year Since Randomization Compared to Baseline, According to Omega-3 Fatty Acid and Placebo Groups, Censoring PHQ-8 Scores at Date of Mood Safety Letter.[a]

| PHQ-8 score | Omega-3 group | | Placebo group | | Mean difference (95% CI) [b] | P-value | P-interaction |
|---|---|---|---|---|---|---|---|
| | Number of participants | Adjusted mean (95% CI) | Number of participants | Adjusted mean (95% CI) | | | |
| Baseline | 9171 | 1.09 (1.06, 1.13) | 9182 | 1.11 (1.08, 1.15) | -- | -- | 0.45 |
| Year 1 vs Baseline | 8471 | 0.05 (0.01, 0.09) | 8549 | 0.01 (-0.02, 0.05) | 0.04 (-0.02, 0.09) | 0.20 | |
| Year 2 vs Baseline | 8320 | 0.08 (0.04, 0.12) | 8340 | 0.05 (0.01, 0.09) | 0.03 (-0.02, 0.09) | 0.25 | |
| Year 3 vs Baseline | 8053 | 0.12 (0.08, 0.16) | 8116 | 0.07 (0.03, 0.11) | 0.05 (-0.01, 0.10) | 0.13 | |
| Year 4 vs Baseline | 7580 | 0.11 (0.07, 0.15) | 7608 | 0.07 (0.03, 0.11) | 0.03 (-0.02, 0.09) | 0.26 | |
| Year 5 vs Baseline | 5210 | 0.22 (0.17, 0.27) | 5188 | 0.23 (0.18, 0.28) | -0.01 (-0.08, 0.06) | 0.77 | |
| Average (across Years 1-5) vs Baseline | 9171 | | 9182 | | 0.03 (-0.01, 0.08) | 0.16 | |

Abbreviation: PHQ, patient health questionnaire; CI, confidence interval

[a] Analyses were from general linear models of response profiles to estimate the means, with time modeled as indicator variables; models were controlled for age, sex, and vitamin D3 randomization group. Adjusted means (95% CI) within each treatment group are

shown at baseline and adjusted mean differences in change (95% CI) within each treatment group are shown for each follow-up time point. P-interaction is from the 5-degree-freedom test of the treatment-x-time interaction term in the model.

[b] Mean differences in change comparing omega-3 fatty acid and placebo groups; the last row shows the adjusted mean difference (95% CI) between the omega-3 fatty acid and placebo groups in PHQ-8 change scores averaged across all follow-up years (years 1-5 vs. baseline).

**Description of Results from Sensitivity Analyses in eTable 10.**

As described in Methods published previously (Okereke et al., JAMA, 2020; Supplement 2, eMethods)[4], enhanced follow-up procedures were instituted for those with elevated PHQ-8 scores. Participants with elevated PHQ-8 scores (≥10 algorithm cutoff) at baseline and follow-up were contacted via mailed letters, where there was no current self-report by the participant of both recent diagnosis and treatment of depression. Among all participants who scored PHQ-8≥15, the same letters were sent regardless of recent self-reported diagnosis or treatment for depression. It was recognized that receipt of a letter intended to raise a participant's awareness of mood problems may influence his or her self-report of mood on a subsequent questionnaire, and this may have potential to bias results. Thus, in this analysis PHQ-8 scores were censored after the date that a mood safety letter was sent (i.e., PHQ-8 responses that occurred after the send date of a mood safety letter did not contribute to the outcome). Results showed that estimates observed in this sensitivity analysis are similar to those in the primary analysis.

**eTable 11.** Adjusted Means at Baseline and Mean Change (95% CI) in PHQ-8 Scores at Each Year Since Randomization Compared to Baseline, According to Omega-3 Fatty Acid and Placebo Groups, Omitting Year 5 PHQ-8 Score.[a]

| PHQ-8 score | Omega-3 group | | Placebo group | | Mean difference (95% CI)[b] | P-value | P-interaction |
|---|---|---|---|---|---|---|---|
| | Number of participants | Adjusted mean (95% CI) | Number of participants | Adjusted mean (95% CI) | | | |
| Baseline | 9171 | 1.09 (1.06, 1.13) | 9182 | 1.11 (1.08, 1.15) | -- | -- | 0.58 |
| Year 1 vs Baseline | 8471 | 0.05 (0.01, 0.09) | 8549 | 0.01 (-0.02, 0.05) | 0.03 (-0.02, 0.09) | 0.21 | |
| Year 2 vs Baseline | 8354 | 0.07 (0.03, 0.11) | 8371 | 0.04 (0.00, 0.08) | 0.02 (-0.03, 0.08) | 0.41 | |
| Year 3 vs Baseline | 8116 | 0.10 (0.06, 0.14) | 8172 | 0.06 (0.02, 0.10) | 0.05 (-0.01, 0.10) | 0.13 | |
| Year 4 vs Baseline | 7676 | 0.08 (0.04, 0.12) | 7690 | 0.05 (0.01, 0.09) | 0.03 (-0.02, 0.09) | 0.26 | |
| Average (across Years 1-4) vs Baseline | 9171 | -- | 9182 | -- | 0.03 (-0.01, 0.08) | 0.13 | |

Abbreviation: CI, confidence interval; PHQ, patient health questionnaire

[a] Analyses were from general linear models of response profiles to estimate the means, with time modeled as indicator variables; models were controlled for age, sex, and vitamin D3 randomization group. Adjusted means (95% CI) within each treatment group are

shown at baseline and adjusted mean differences in change (95% CI) within each treatment group are shown for each follow-up time point. P-interaction is from the test of the treatment-x-time interaction term in the model.

[b] Mean differences in change comparing omega-3 fatty acid and placebo groups; the last row shows the adjusted mean difference (95% CI) between the omega-3 fatty acid and placebo groups in PHQ-8 change scores averaged across all follow-up years (years 1-4 vs. baseline).

**eTable 12.** Total, Incident and Recurrent Rates of Depression, per 1000 Person-Years (p-y), by Omega-3 Fatty Acid and Placebo Groups.

| **Omega-3 group** | | | |
|---|---|---|---|
| Outcome | Number of participants | Cases | Per 1000 p-y |
| Total depression[a] | 9171 | 651 | 13.9 |
| Incident depression[b] | 8322 | 493 | 11.5 |
| Recurrent depression[b] | 849 | 158 | 38.8 |
| **Placebo group** | | | |
| Outcome | Number of participants | Cases | Per 1000 p-y |
| Total depression[a] | 9182 | 583 | 12.3 |
| Incident depression[b] | 8335 | 427 | 9.9 |
| Recurrent depression[b] | 847 | 156 | 38.2 |

[a] Depression is a composite outcome comprising reported presence of clinician diagnosis of depression, treatment for depression and/or symptoms above the validated cutoff for major depression on the PHQ-8 (PHQ-8≥10); total depression consists of all incident and recurrent depression combined.

[b] Incident and recurrent depression were exploratory outcomes. Incident depression was defined as depression cases that occurred among those with no past history of depression; recurrent depression was defined as depression cases that occurred among those with past history of depression, but not under treatment or active in the past 2 years.

**eTable 13.** Means (SDs) of PHQ-8 Scores at Each Time Point, in Omega-3 Fatty Acid and Placebo Groups.

| Time | Omega-3 group | Placebo group |
|---|---|---|
| Baseline | 1.09 (1.60) | 1.11 (1.62) |
| Year 1 | 1.12 (1.95) | 1.11 (1.89) |
| Year 2 | 1.13 (2.02) | 1.13 (1.94) |
| Year 3 | 1.15 (2.04) | 1.13 (1.96) |
| Year 4 | 1.12 (1.98) | 1.11 (1.93) |
| Year 5 | 1.21 (2.06) | 1.25 (2.10) |

Abbreviation: PHQ, patient health questionnaire

**eTable 14a.** Hazard Ratios and 95% CIs for Total, Incident, and Recurrent Depression among Older Males, According to Randomized Assignment to Omega-3 Fatty Acid or Placebo Groups.[a]

| Outcome | Omega-3 group | Placebo group | HR (95% CI) | P-value |
|---|---|---|---|---|
| | *Event/no. of participants* | | | |
| Incident depression[b] | 208/4305 | 218/4337 | 0.96 (0.80 - 1.17) | 0.71 |
| Recurrent depression[b] | 64/369 | 58/319 | 0.94 (0.66 - 1.34) | 0.74 |

Abbreviation: HR, hazard ratio; CI, confidence interval

[a] Analyses were from Cox regression models that were controlled for age, sex, and vitamin D3 randomization group. Analyses were not adjusted for multiple comparisons.

[b] Incident and recurrent depression were exploratory outcomes. Incident depression was defined as depression cases that occurred among those with no past history of depression; recurrent depression was defined as depression cases that occurred among those with past history of depression, but not under treatment or active in the past 2 years.

**eTable 14b.** Hazard Ratios and 95% CIs for Total, Incident, and Recurrent Depression among Older Females, According to Randomized Assignment to Omega-3 Fatty Acid or Placebo Groups.[a]

| Outcome | Omega-3 group | Placebo group | HR (95% CI) | P-value |
|---|---|---|---|---|
| | *Event/no. of participants* | | | |
| Incident depression[b] | 285/4017 | 209/3998 | 1.38 (1.15 - 1.65) | <0.001 |
| Recurrent depression[b] | 94/480 | 98/528 | 1.06 (0.80 - 1.40) | 0.70 |

Abbreviation: HR, hazard ratio; CI, confidence interval

[a] Analyses were from Cox regression models that were controlled for age, sex, and vitamin D3 randomization group. Analyses were not adjusted for multiple comparisons.

[b] Incident and recurrent depression were exploratory outcomes. Incident depression was defined as depression cases that occurred among those with no past history of depression; recurrent depression was defined as depression cases that occurred among those with past history of depression, but not under treatment or active in the past 2 years.

**eTable 15.** Hazard Ratios and 95% CIs for Total, Incident, and Recurrent Depression, According to Randomized Assignment to Omega-3 Fatty Acid or Placebo, Excluding the First 2 Years of Follow-up.[a]

| Outcome | Omega-3 group | Placebo group | HR (95% CI) | P-value |
|---|---|---|---|---|
| | *Events/no. of participants* | | | |
| Total depression[b] | 395/8845 | 370/8906 | 1.08 (0.94 – 1.25) | 0.27 |
| Incident depression[c] | 303/8067 | 280/8127 | 1.10 (0.93 – 1.29) | 0.26 |
| Recurrent depression[c] | 92/778 | 90/779 | 1.02 (0.76 – 1.37) | 0.88 |

Abbreviation: HR, hazard ratio; CI, confidence interval

[a] Analyses were from Cox regression models that were controlled for age, sex, and vitamin D3 randomization group. Events occurring in the first 2 years of follow-up were excluded. Analyses were not adjusted for multiple comparisons.

[b] Depression is a composite outcome comprising reported presence of clinician diagnosis of depression, treatment for depression and/or symptoms above the validated cutoff for major depression on the PHQ-8 (PHQ-8≥10); total depression consists of all incident and recurrent depression combined.

[c] Incident and recurrent depression were exploratory outcomes. Incident depression was defined as depression cases that occurred among those with no past history of depression; recurrent depression was defined as depression cases that occurred among those with past history of depression, but not under treatment or active in the past 2 years.

**eTable 16.** Hazard Ratios and 95% CIs of Total, Incident, and Recurrent Depression among Participants with Mild Depressive Symptoms, According to Randomized Assignment to Omega-3 Fatty Acid or Placebo Groups.[a]

| Outcome | Omega-3 group | Placebo group | HR (95% CI) | P-value |
|---|---|---|---|---|
| | *Event/no. of participants* | | | |
| Total depression[b] | 77/267 | 73/268 | 1.09 (0.79 - 1.50) | 0.60 |
| Incident depression[c] | 51/216 | 53/214 | 0.96 (0.66 - 1.42) | 0.85 |
| Recurrent depression[c] | 26/51 | 20/54 | 1.55 (0.86 - 2.80) | 0.15 |

Abbreviation: HR, hazard ratio; CI, confidence interval

[a] PHQ-8 score between 5-9 points were used to define mild depressive symptoms. Analyses to compute HRs and CIs were from Cox regression models that were controlled for age, sex, and vitamin D3 randomization group.

[b] Depression is a composite outcome comprising reported presence of clinician diagnosis of depression, treatment for depression and/or symptoms above the validated cutoff for major depression on the PHQ-8(PHQ-8≥10); total depression consists of all incident and recurrent depression combined.

[c] Incident and recurrent depression were exploratory outcomes. Incident depression was defined as depression cases that occurred among those with no past history of depression; recurrent depression was defined as depression cases that occurred among those with past history of depression, but not under treatment or active in the past 2 years.

**eTable 17.** Adjusted Means at Baseline and Mean Change (95% CI) in PHQ-8 Scores at Each Year Since Randomization Compared to Baseline, According to Omega-3 Fatty Acid and Placebo Groups, among Participants with Mild Depressive Symptoms.[a]

| PHQ-8 score | Omega-3 group | | Placebo group | | Mean difference (95% CI) [b] | P-value | P-interaction |
|---|---|---|---|---|---|---|---|
| | Number of participants | Adjusted mean (95% CI) | Number of participants | Adjusted mean (95% CI) | | | |
| Baseline | 267 | 6.81 (6.69, 6.93) | 268 | 6.95 (6.82, 7.08) | -- | -- | 0.34 |
| Year 1 vs Baseline | 237 | -2.35 (-2.82, -1.88) | 233 | -2.80 (-3.25, -2.35) | 0.45 (-0.20, 1.10) | 0.18 | |
| Year 2 vs Baseline | 224 | -2.13 (-2.69, -1.58) | 217 | -2.86 (-3.30, -2.43) | 0.73 (0.03, 1.43) | 0.04 | |
| Year 3 vs Baseline | 217 | -2.44 (-2.91, -1.96) | 218 | -2.74 (-3.21, -2.28) | 0.31 (-0.36, 0.98) | 0.37 | |
| Year 4 vs Baseline | 197 | -2.42 (-2.94, -1.90) | 192 | -2.52 (-3.05, -1.99) | 0.10 (-0.64, 0.84) | 0.79 | |
| Year 5 vs Baseline | 138 | -2.48 (-3.06, -1.90) | 130 | -2.36 (-3.01, -1.72) | -0.12 (-0.99, 0.75) | 0.79 | |
| Average (across Years 1-5) vs Baseline | 267 | | 268 | | 0.31 (-0.21, 0.83) | 0.24 | |

Abbreviation: PHQ, patient health questionnaire; CI, confidence interval

[a] PHQ-8 score between 5-9 points were used to define mild depressive symptoms. Analyses were from general linear models of response profiles to estimate the means, with time modeled as indicator variables; models were controlled for age, sex, and vitamin D3

randomization group. Adjusted means (95% CI) within each treatment group are shown at baseline and adjusted mean differences in change (95% CI) within each treatment group are shown for each follow-up time point. P-interaction is from the 5-degree-freedom test of the treatment-x-time interaction term in the model.

[b] Mean differences in change comparing omega-3 fatty acid and placebo groups; the last row shows the adjusted mean difference (95% CI) between the omega-3 fatty acid and placebo groups in PHQ-8 change scores averaged across all follow-up years (years 1-5 vs. baseline).

**eTable 18.** Adverse Events According to Omega-3 Fatty Acid and Placebo Groups.[a]

| | **Omega-3 group** | **Placebo group** |
|---|---|---|
| | **Affected/at Risk (%)** | **Affected /at Risk (%)** |
| **Serious Adverse Events** | | |
| Major cardiovascular event[b] | 249/9171 (2.7%) | 270/9182 (2.9%) |
| Invasive cancer of any type | 613/9171 (6.7%) | 572/9182 (6.2%) |
| All-cause mortality | 305/9171 (3.3%) | 286/9182 (3.1%) |
| Gastrointestinal bleeding | 240/9171 (2.6%) | 246/9182 (2.7%) |
| Hypercalcemia | 91/9171 (1.0%) | 100/9182 (1.1%) |
| Suicide | 2/9171 (0.02%) | 1/9182 (0.01%) |
| **Other Adverse Events** | | |
| Parathyroid condition[c] | 27/9171 (0.3%) | 46/9182 (0.5%) |
| Kidney stones | 289/9171 (3.2%) | 335/9182 (3.6%) |

| | **Omega-3 group** | **Placebo group** |
|---|---|---|
| | **Affected/at Risk (%)** | **Affected /at Risk (%)** |
| Kidney failure | 47/9171 (0.5%) | 56/9182 (0.6%) |
| Blood in urine | 626/9171 (6.8%) | 637/9182 (6.9%) |
| Easy bruising | 2276/9171 (24.8%) | 2308/9182 (25.1%) |
| Frequent nosebleeds | 317/9171 (3.5%) | 322/9182 (3.5%) |
| Stomach upset or pain | 3231/9171 (35.2%) | 3219/9182 (35.1%) |
| Skin rash | 2293/9171 (25.0%) | 2289/9182 (24.9%) |

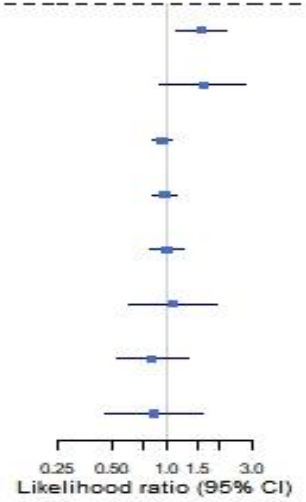
[a] Adverse events were ascertained systematically throughout the trial on study questionnaires.

[b] Major cardiovascular event was a composite outcome of myocardial infarction, stroke, and death from cardiovascular causes.

[c] Parathyroid condition includes hyperparathyroidism or hypoparathyroidism.

**eFigure 1.** Adjusted Differences in Change in Likelihood of PHQ-8 Item-Level Symptoms, Comparing Omega-3 Fatty Acid to Placebo.[a]

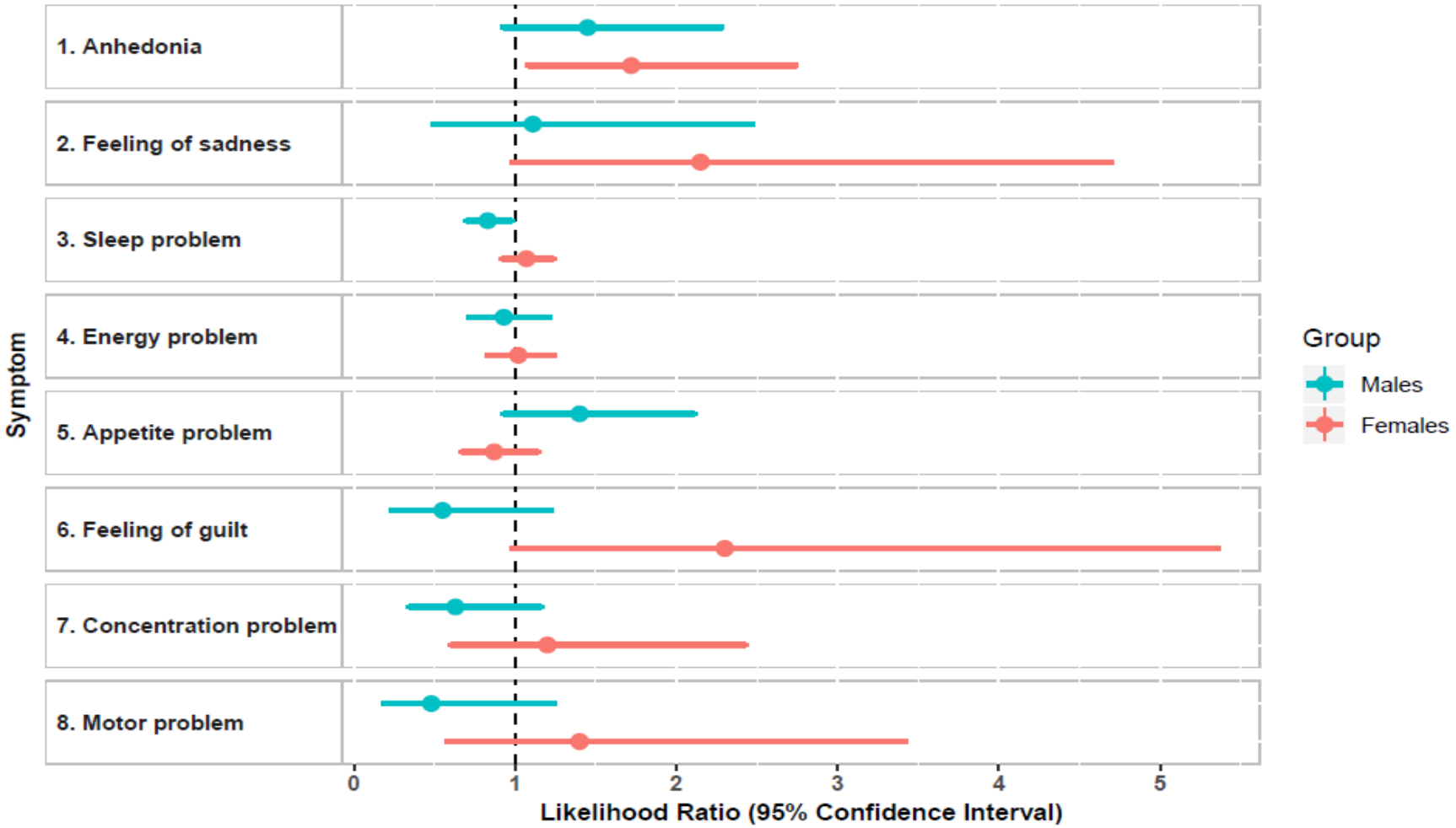
| Item-level symptom | Likelihood ratio (95% CI) | P-value |
|---|---|---|
| Anhedonia | 1.58 (1.14-2.18) | 0.006 |
| Feeling of sadness | 1.60 (0.92-2.80) | 0.10 |
| Sleep problems | 0.95 (0.85-1.07) | 0.39 |
| Energy problems | 0.98 (0.84-1.15) | 0.81 |
| Appetite problems | 1.01 (0.81-1.26) | 0.93 |
| Feeling of guilt | 1.10 (0.62-1.94) | 0.74 |
| Concentration problems | 0.83 (0.53-1.32) | 0.43 |
| Motor problems | 0.85 (0.45-1.61) | 0.62 |




Abbreviation: CI, confidence interval; PHQ, patient health questionnaire

[a] Analyses were from repeated measures logistic regression models, with follow-up time modeled as an indicator; models were controlled for age, sex, and vitamin D3 randomization group. Results show likelihood ratios and 95% confidence intervals (95% CIs), which reflect differences in the change in likelihood of burden from each PHQ-8 item-level symptom, comparing omega-3 fatty acid to placebo treatment group. Differences reflect the average effect over all follow-up times since baseline.

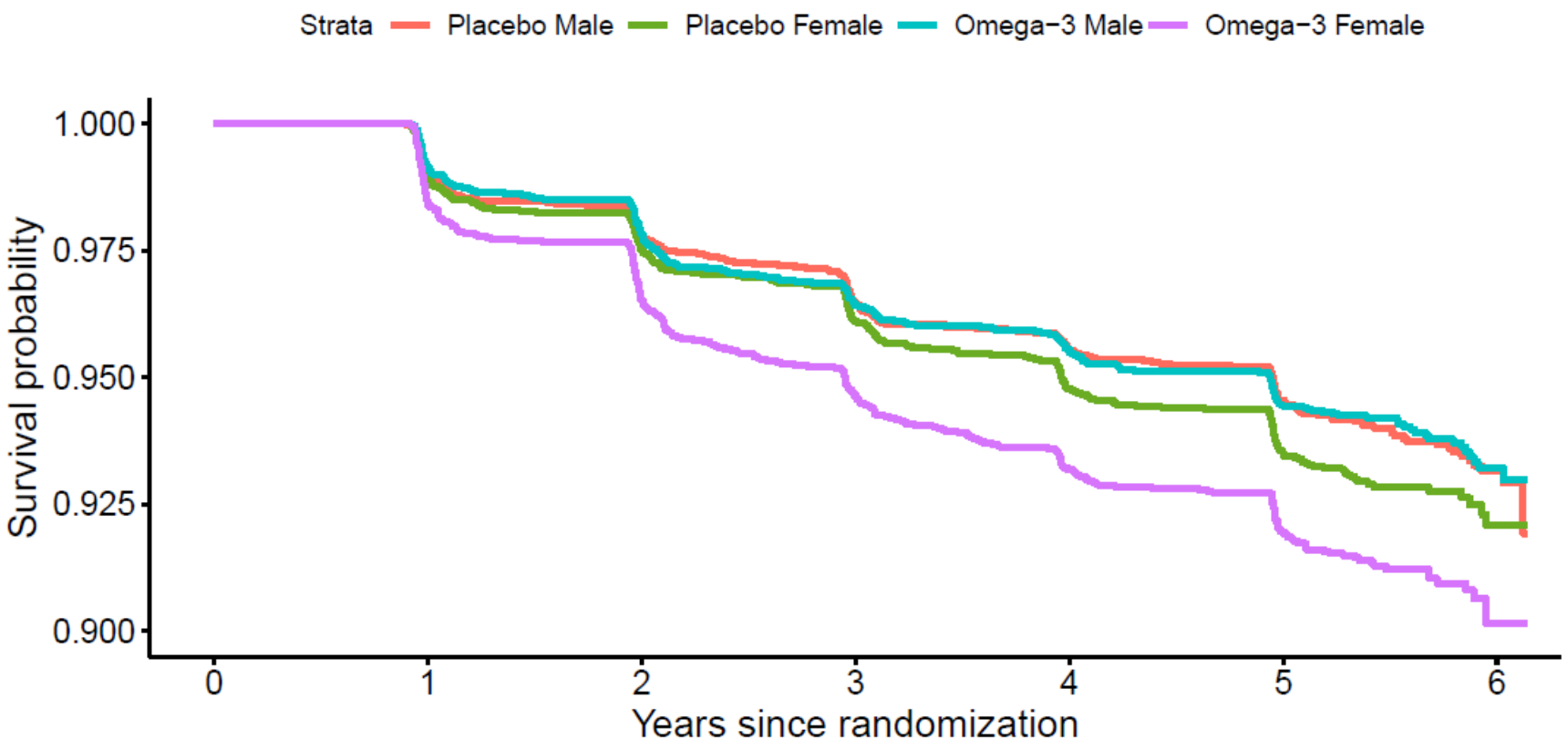
**eFigure 2.** Adjusted Differences in Change in Likelihood of PHQ-8 Item-Level Symptoms, Comparing Omega-3 Fatty Acid to Placebo, Stratified by Biological Sex.[a]



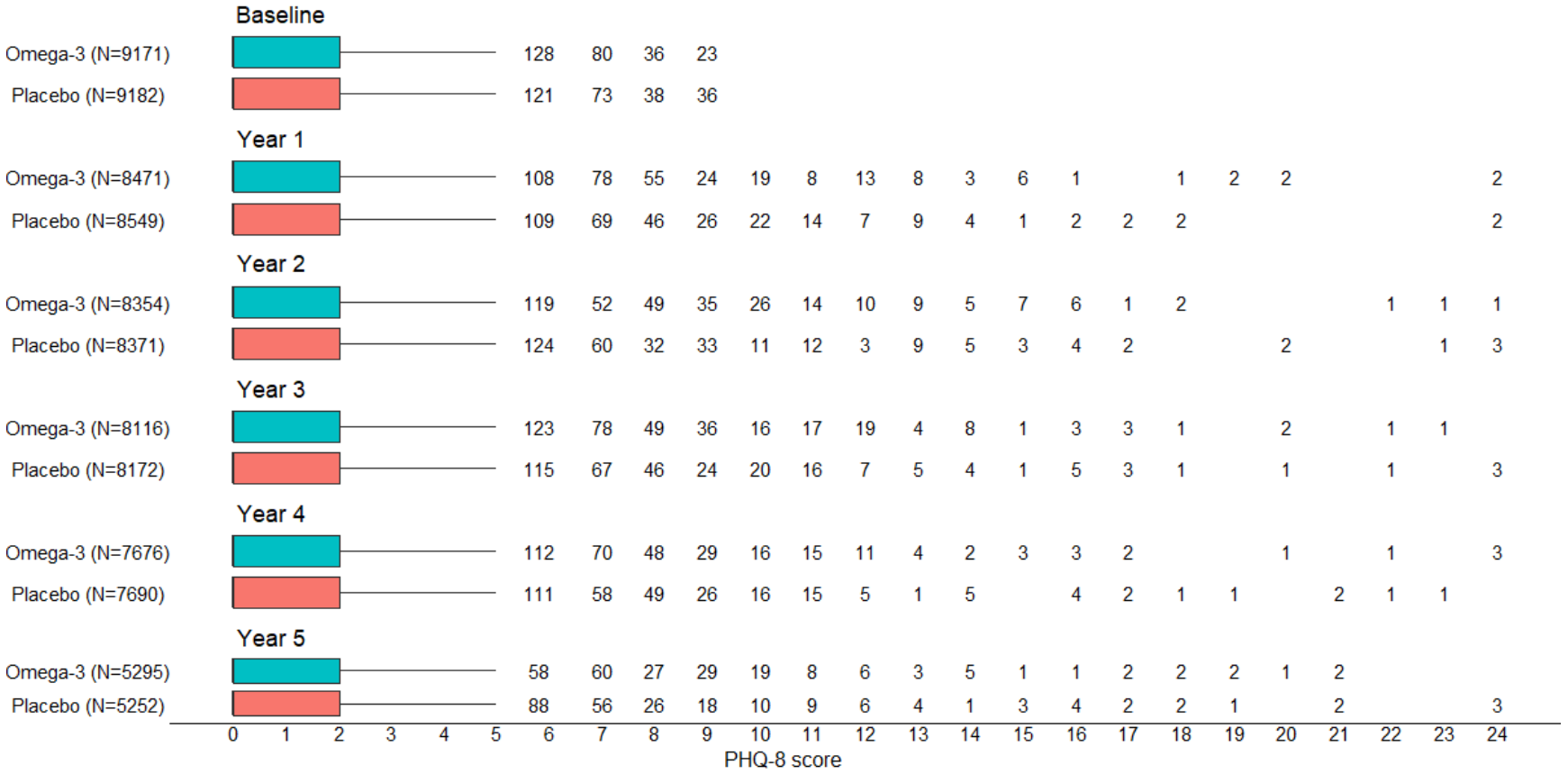

Abbreviation: CI, confidence interval; PHQ, patient health questionnaire

[a] Analyses were from repeated measures logistic regression models stratified by sex, with follow-up time modeled as an indicator; models were controlled for age, sex, and vitamin D3 randomization group. Results show likelihood ratios and 95% CIs, which reflect differences in the change in likelihood of burden from each PHQ-8 item-level symptom among males and females, comparing omega-3 fatty acid to placebo treatment group. Differences reflect the average effect over all follow-up times since baseline.

**eFigure 3**. Kaplan-Meier Survival Curves Stratified by Biological Sex for Time since Randomization until Occurrence of Primary Outcome (Total Depression), in Omega-3 Fatty Acid and Placebo Groups.



**eFigure 4**. Box Plots of Crude PHQ-8 Scores in the Omega-3 Fatty Acid and Placebo Groups in Each Study Year.[a]




Abbreviation: PHQ, patient health questionnaire

[a] The figure illustrates two horizontal box plots for each study year, with the crude distributions of PHQ-8 scores in the omega-3 fatty acid and placebo groups by study year. The figure also illustrates the number of participants (in the outlier portions of the box plots) at each value of PHQ-8 score in the omega-3 fatty acid and placebo groups.

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