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# Supplementary Material

**Article Title:** Effects of Vitamin D3 and Marine Omega-3 Fatty Acids Supplementation on Indicated and Selective Prevention of Depression in Older Adults: Results From the Clinical Center Sub-Cohort of the VITamin D and OmegA-3 TriaL (VITAL)

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**Appendix 1: Supplementary Methods**

**A. Changes to the study protocol**

VITAL-DEP (VITamin D and OmegA-3 TriaL - Depression Endpoint Prevention),[1-3] an ancillary study to VITAL,[4-6] was initially funded in 2010; changes that occurred since then in the statistical analysis plan (SAP) have been outlined previously.[2] This study presents results from the secondary aims of the VITAL-DEP protocol. In this study, among a deeply-phenotyped sub-set of VITAL-DEP (n=720) participants, we determined effects of vitamin D3 and marine omega-3 fatty acids (omega-3s) on indicated and selective prevention of late-life depression (LLD). Below we provide study protocol changes related to testing of these aims.

The SAP described that regression-based survival methods will be used to test whether there are significant differences between treatment agents vs. placebos in risk of incident major depressive disorder (MDD), stratified by risk groups of indicated and selective prevention. Power calculations were based on plausible estimates for numbers of persons-at-risk in published observational studies of late-life depression, as well as risk ratios for treatment effects in previously published randomized trials of indicated and selective prevention of LLD; investigators have reported that successful indicated and selective preventive interventions can reduce MDD risk in older adults by up to 50-60%.[7-10] However, incident MDD events were lower (~5%) than expected in this study. Thus, the Cox-proportional hazard regression analyses planned per the SAP would be hampered when event rates are small, leading potentially to results that are inaccurate or misleading.[11] Therefore, we used exact chi-square test statistics to compare effects between treatment agents vs. their matching placebos, on risk of incident MDD among those with or without subthreshold depression (indicated

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prevention) or with or without ≥1 high-risk factors for LLD (selective prevention); relative risk (RR) estimates and exact 95% confidence intervals (CIs) were presented. The Zelen exact test was used to determine whether effects of treatment agents differed across the risk groups of indicated and selective prevention. Moreover, due to low events, our study was underpowered to compute an adjusted risk ratio of incident MDD for indicated and selective prevention.

This study has two pre-specified co-primary outcomes: 1) risk of incident MDD and 2) change in mood score. We acknowledged in the SAP that although these primary outcomes are separate, one may affect the other. The presence of two primary outcomes may cause inflation of Type I error if each of the two outcomes is tested at alpha=0.05. Thus, the Bonferroni corrections have been applied to divide equally the total available alpha among the pre-specified primary outcomes – i.e., 0.05/2 = 0.025 was used for the significance threshold for each of the primary outcomes.

**B. Extensive research team training**

The VITAL-DEP protocol involved a wide array of on-site research activities (including in-person interactions with study participants), which invariably require extensive training for research assistants (RAs). Two of the study psychiatrists (Drs. Okereke and Mischoulon) organized periodic, rigorous refresher training sessions for RAs to enhance their interpersonal and communication skills, as well as their ability to administer the Mini-International Neuropsychiatric Interview (MINI) for the DSM (Diagnostic and Statistical Manual)-IV[12] and neuropsychological testing and to conduct proper scoring of all cognitive tests and self-report measures

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[e.g., the Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder-7 (GAD-7), Modified Mini-Mental State Exam (3MS), etc.]. In these training sessions, the RAs were presented different clinical case scenarios and trained to ensure their ability: i) to identify psychiatric core and supporting features on the MINI modules as well as unstable psychiatric symptoms (e.g., suicidal ideation or psychotic symptoms); ii) to differentiate symptom presentations of different psychiatric disorders (e.g., depression episode in bipolar disorder vs. in major depressive disorder); iii) to assess for "rule out" of potential medical causes for psychiatric diagnoses; iv) to score properly and respond appropriately to the MINI suicidality module or suicidal ideation symptoms [e.g., a score of 3 on suicide item-level symptom (item #9 on PHQ-9), endorsement of the suicide item on the MINI MDD module, or score of ≥6 on the MINI suicidality module]; v) to page a study psychiatrist (Drs. Okereke, Mischoulon or Chang) for participants who were determined to have serious suicidal risk or unstable psychiatric symptoms (see under C. Enhanced Safety Procedures); vi) to provide participants determined to be experiencing a major depressive episode, but not unstable symptoms, with additional information and resources related to depression education and care. At the end of training sessions, RAs were required to illustrate satisfactory performance, in the opinion of Drs. Okereke and Mischoulon, of the above skills during the real-time exercises using clinical scenarios. All RAs were also required to achieve a passing score on the knowledge test for the 3MS (i.e., the 3MS "quiz") that was part of the neuropsychological testing.

A series of quality control steps were performed to prevent rating errors and interviewing mistakes during in-person assessments: i) after completion of each CTSC interview, the diagnostic rating scoresheets completed by each RA was independently verified by

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another RA in the CTSC; ii) the senior RAs were trained to (re-)verify diagnostic interview scoresheets and identify any potential scoring inaccuracies, which were then directly reviewed with PI Dr. Okereke before final scoresheets were sent for computer scanning; iii) the study psychiatrists performed periodic CTSC audits to ensure the quality of interviews and in-person assessments; during these audits, Dr. Okereke or Dr. Mischoulon observed the RAs during the completion of the entire VITAL-DEP CTSC protocol with participants and the raw testing packets and score sheets were examined for accuracy.

**C. Enhanced safety procedures**

As our study featured in-person assessments using gold-standard psychiatric interviews, we recognized the need for implementing enhanced safety measures during the CTSC visit. As described above, study participants were administered the MINI for the DSM-IV, which is validated for time-efficient determinations of safety and diagnostic status for both eligibility and outcome purposes.[12] The DSM-IV was utilized in this study, as the VITAL-DEP study application was submitted and awarded by the funding agency in 2010 – three years prior to the publication of the DSM-5.[13] Within the CTSC, the administration of the MINI, along with the PHQ-9, allowed for real-time assessments of symptoms that may indicate safety risks. In the event that a participant reported symptoms meeting the threshold of suicide risk alert (as noted above), or reported other unstable psychiatric symptoms (e.g., homicidality, mania, current psychosis), the RA was instructed to page a study psychiatrist for an immediate evaluation of participants presenting with those symptoms and determination of their safety, appropriate disposition, and ability to participate further in the study. If a participant was determined by on-call MD to have serious suicidal ideation or serious risk for suicide or to be otherwise unsafe due to the presence of

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other unstable psychiatric symptoms, he/she was discontinued from the VITAL-DEP CTSC study and provided assistance with further management of their symptoms (e.g., contact primary care physicians and/or local mental health providers).

**D. Assessment of interrater reliability for adjudication of MDD**

Ms. Weinberg randomly selected 60 MDD case adjudication files and allocated them to the CTSC study psychiatrists (Dr. Okereke, Dr. Mischoulon, Dr. Chang); as raters, the study psychiatrists completely their adjudications independently and were blinded to the original case diagnoses (copies of raw testing packets were prepared such that initial diagnoses were obscured). There was strong agreement among the study psychiatrists with respect to the diagnosis of incident MDD. The majority of adjudications had been completed by two psychiatrists; the level of agreement (i.e., kappa) ranged from 0.72-1.0 for current and past MDD diagnoses.

**E. Approach for selective prevention**

We classified participants for selective prevention using well-validated measures at baseline. The risk group for selective prevention included participants with vs. without ≥1 high-risk factors for late-life depression. The risk factors were selected based on robust prior literature on late-life depression risk architecture.[14-16] The selected high-risk factors for late-life depression included: subthreshold or clinical anxiety, impaired activities of daily living, physical/functional limitation, medical comorbidity, cognitive impairment, problem drinking, caregiving burden, and low psychosocial support. The evidence-based methodological approach used for characterizing participants for the individual risk factor is provided below.

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1) Subthreshold or clinical anxiety: Generalized Anxiety Disorder (GAD) scale, a 4-point Likert scale (0=not at all, 1=several days, 2=more than half the days, 3=nearly every day), was used to define subthreshold anxiety.[17,18] Adjudicated diagnoses of DSM-IV anxiety disorders (such as agoraphobia, GAD, panic disorder, social phobia) were used to define clinical anxiety. The presence of subclinical or clinical anxiety at baseline was defined using a Boolean variable of presence of elevated anxiety symptoms (GAD-2 score ≥3 or GAD-7 score ≥5) and/or any adjudicated DSM-IV diagnoses of anxiety disorders.

2) Impaired activities in daily living: We used a validated 6-item, 3-point IADL (Instrumental Activity of Daily Living) scale (0=yes, without help, 1=yes, with some help, 2=no, unable to do this activity) to assess the status of functional impairment in IADLs.[19] For each item, we combined responses on higher categories (i.e., 1=yes, with some help, 2=no, unable to do this activity). A binary variable was computed (0=no, 1=yes). Then, the IADL score was computed by summing up all the items (range: 0-6 points). Impairment in IADLs was defined by an IADL score of ≥1 point.

3) Physical/functional limitation: The PF-10 is part of the Medical Outcomes Study Short Form-36 (SF-36); this 10-item physical functioning scale covers a broad range of aspects of subjective physical function, ranging from activities of daily living such as bathing and dressing to rigorous activities such as running and lifting heavy objects.[20] Repeated measures of the PF-10 were obtained on the main VITAL cohort questionnaires, including at baseline. Each PF-10 item has the same three response choices; each answer of

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"Yes, limited a lot" is assigned one point, an answer of "Yes, limited a little" is assigned two points, and an answer of "No, not limited at all" is assigned three points. A raw score is derived from the set of 10 questions and ranges from a minimum of 10 points to a maximum of 30 points. The raw score is then transformed to a 100-point scale, with a score of 100 considered the highest physical function. The PF-10 scale has been extensively utilized and validated in other longitudinal studies of older adults.[21,22]

4) Medical comorbidity: Information on self-reported medical conditions was collected on the main VITAL cohort baseline questionnaire. Medical comorbidity burden was derived summing the count of major comorbid medical conditions (1+ vs. 0). The list of medical conditions included diabetes, cardiac failure, severe liver disease, chronic obstructive pulmonary disorder, Parkinson disease, rheumatoid arthritis, inflammatory bowel disorders, polymyalgia rheumatica, intermittent claudication, carotid stenting or stenosis, and multiple sclerosis. Of note, VITAL participants were free of any prior history of cardiovascular disease (e.g., myocardial infarction, stroke, coronary artery bypass grafting) or cancer (except non-melanoma skin cancer) at enrollment. Additional safety exclusions were: renal failure or dialysis, cirrhosis, hyperparathyroidism, sarcoidosis or granulomatous disease, fish/seafood allergy, anticoagulant use, or serious conditions.[4]

5) Cognitive impairment: Detailed neuropsychiatric testing was conducted as per the protocol; details are published elsewhere.[1,23] Cognitive tests included: The Modified Mini-Mental State (3MS) for general cognition;[24] immediate and delayed recall trials of a word list and the East Boston Memory Test paragraph[25] and two category fluency tests (animal and vegetable)[26] for verbal memory;

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and trail-making tests (Trails-A and Trails-B for executive function and psychomotor speed, respectively).[27] All VITAL-DEP CTSC eligible participants were administered the HHIE-S (Hearing Handicap Inventory for the Elderly-Screening)[28] to determine hearing impairment. Participants who scored at >50% likelihood of significant hearing impairment were administered the 3MS, but not the other cognitive tests. We used the 3MS to determine cognitive impairment since it was available on all participants. As VITAL is a racially/ethnically diverse cohort, we used norm-based cut-offs that account for age, sex, race/ethnicity, and education, for identifying the presence of dementia-level cognitive impairment: <92 among non-Hispanic men; <95 among non-Hispanic women; <89 among Black and Hispanic men and women; <91 among Asian and other-race reporting men and women.[29]

6) Problem drinking: The AUDIT-C (The Alcohol Use Disorders Identification Test-Concise),[30] a 3-item alcohol screening instrument, was used to characterize problem drinking. On the MINI, all participants were asked about core features (i.e., gating questions) of DSM-IV alcohol dependence or abuse. Problem drinking was defined using a Boolean variable of 'yes' response on core features of alcohol use disorders and/or AUDIT-C ≥5 points, as there is no configuration of AUDIT-C responses that could generate a total score of 5 or more points and not involve heavy or problem drinking patterns. In the literature, we recognize that investigators used the AUDIT-C cut-off of ≥4 points for *screening* older adults for problem drinking.[31,32] In this trial, our focus is to determine older adults who were actually *at-risk* for problem drinking; a more specific approach is warranted. Using a slightly higher AUDIT-C cut-off (i.e., ≥5 points) will minimize the possibility of participants being misclassified at risk for problem drinking. Of note, 4 drinks/week can be common among older adults who were following Mediterranean dietary patterns.

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7) Caregiving burden: The short-form Zarit Burden Interview-12 (Zarit-12)[33] was used to determine caregiving burden; participants were asked about caregiving regularly provided to relatives, friends, or other loved ones. Among participants who reported that they were providing caregiving, we computed the Zarit-12 score by summation of 12 items (0 to 4 points per item: 0=never, 1=rarely, 2=sometimes, 3=quite frequently, 4=nearly always; score range: 0-48 points; 0-10 points: mild burden, 10-20: mild-to-moderate burden, >20: high burden). Participants also self-reported an overall rating for presence of caregiving burden on the same questionnaire (i.e., "not at all", "a little", "moderately", "quite a bit", "extremely"). The presence of caregiving burden was defined using a Boolean variable of ≥10 points on ZARIT score (>mild burden) and/or self-reported rating of moderately or higher caregiving burden.

8) Low psychosocial support: The Duke Social Support Index (DSSI)[34] was used to assess psychosocial support. The DSSI score (range: 0-33 points) was calculated as the sum of responses on 11 Likert-scaled items, with mean imputation for up to two missing items. The cut-off ≤26 points was used for low psychosocial support.[35,36]

**F. Objective physical performance measures**

VITAL-Bone health, an ancillary study to VITAL, conducted comprehensive assessments of objective physical performance during CTSC visits; protocol details have been published elsewhere.[37] The Short Physical Performance Battery (SPPB; components include

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walking speed, standing balance, and chair stands)[38] and the Timed Up and Go (TUG) test[39] were assessed. The composite SPPB score (range: 0-12 points) was determined by scoring normal everyday walking speed, standing balance, and chair stands on a scale of 0-4 points.[40,41] A higher SPPB score denotes high physical function. The TUG is a timed test that consists of standing up from a chair, walking 3 meters, turning around, and returning to sit in the chair. Slow TUG denotes low physical function. In this sample (n=720), there were 538 (74.7%) and 461 (64.0%) participants who also completed the SPPB and TUG test, respectively. The median (range) SPPB score was 10.0 (2.0-12.0), and median (range) TUG score was 7.7 (2.8-14.1) seconds.

**G. Validity checks for subjective physical function**

In the literature,[14-16] physical/functional limitation has been reported as the single largest non-affective contributor to risk of LLD, and the PF-10 was used to identify physical/functional limitation in this study. Therefore, although the PF-10 has been extensively utilized and validated elsewhere, it was important to confirm its validity specifically in our own sample. As described above, in-person assessments of objective physical function were conducted as a part of the VITAL-Bone health sub-study.[37] These objective measures were available, however, in a smaller subset of our participants – unlike the PF-10, which had been ascertained in >94% of participants. As detailed below, we conducted a series of validity checks for self-reported physical function.

1) <u>Correlations between subjective and objective physical function measures</u>

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We computed Spearman rank correlations between PF-10 and objective physical function test scores; results are shown in Supplementary Table 7. When the PF-10 score was compared with objective physical function measures, modest significant positive correlations were found for SPPB [spearman rho ($\rho$)=0.36, $p<0.001$]; negative correlations for TUG ($\rho$= -0.36; $p<0.001$).

2) Concordance analyses between subjective and objective physical function measures

We calculated absolute agreement and the kappa statistic for chance-corrected agreement between the PF-10 and either the SPPB or TUG, based on classifying persons as impaired vs. not impaired. Among older adults in the EPESE (Established Populations for Epidemiologic Studies of the Elderly) study, Guralnik et al.[42] determined three cut-points of SPPB summary performance score for physical impairment: >10: normal performance; 7-9 possible limitation; ≤6: presence of disability. For validation purposes, an SPPB cut-point of 10 was used to define the presence of physical impairment, and concordance analysis between PF-10 and SPPB categories was calculated; the absolute agreement was 73.6% and chance-corrected agreement was modest [kappa coefficient ($\kappa$) = 0.32, 95% CI: (0.23-0.41)]. Regarding TUG, the optimal cut-point for determining the presence of physical/functional limitation in community-dwelling older adults is unclear. Garber et al.[43] found that TUG ≤8.5 could be considered for normal physical function in diverse, well-characterized older adults. Therefore, using TUG >8.5 to classify presence of physical impairment, the absolute agreement between PF-10 and TUG was 77.2% and the chance-corrected agreement was modest and similar to that observed for the SPPB [$\kappa$ = 0.33, 95% CI: (0.22 - 0.43)]. Of note, the PF-10 scale measures overall physical function, while SPPB and TUG tests are used for

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assessing lower extremity function. This may explain the consistent, statistically significant correlations across measures but moderate kappas between PF-10 and the SPPB and TUG.

3) Concurrent validity of subjective physical function

We found evidence that the PF-10 scale and SPPB tests were concurrently related to each other. The distribution of the SPPB was compared with the self-reported PF-10 individual items (Supplementary Table 8); for all items, participants who reported low physical function had significantly lower SPPB summary performance scores compared to those who had reported normal physical function.

4. Correlation between subjective physical function and self-reported physical activity

As an additional validity check, we computed Spearman correlations between the PF-10 score with physical activity. In this sample, we observed a positive Spearman rank correlation between the PF-10 score and physical activity [measured in metabolic equivalent of task (MET)-hours/week] ($\rho=0.29$, $p<0.01$).

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**Supplementary Table 1. Participant-reported adherence with vitamin D3, omega-3s, or their matching placebos over the 2-year follow-up.[a]**

1) Vitamin D3 vs. placebo

| | | Vitamin D3 | Placebo |
|---|---|---|---|
| Time | N | % | % |
| 6 Months | 707 | 98.3 | 97.5 |
| 1 Year | 713 | 96.9 | 97.5 |
| 2 Years | 704 | 95.4 | 94.4 |

2) Omega-3s vs. placebo

| | | Omega-3s | Placebo |
|---|---|---|---|
| Time | N | % | % |
| 6 Months | 707 | 99.4 | 97.8 |
| 1 Year | 713 | 96.8 | 98.1 |
| 2 Years | 704 | 95.0 | 95.3 |

[a] N and percentages are shown for those participants answering the compliance questions by questionnaire; during the 2-year CTSC follow-up period, VITAL compliance cards were sent at 6-month, 1-year and 2-year follow-up.[44] Adherence to trial regimen was assessed as the percentage of participants who reported taking at least two-thirds of the study pills.

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**Supplementary Table 2. Detailed baseline characteristics of sample, according to assignment to randomized group.[a]**

| Characteristics | Total sample (n=720) | Active vitamin D3 and active omega-3s (n=176) | Active vitamin D3 and placebo omega-3s (n=178) | Placebo Vitamin D3 and active omega-3s (n=176) | Placebo Vitamin D3 and placebo omega-3s (n=190) |
|---|---|---|---|---|---|
| Age at CTSC visit, Mean (SD), years | 65.4 (6.5) | 65.3 (6.3) | 65.2 (6.2) | 65.5 (7.0) | 65.4 (6.7) |
| Sex, n (%) | | | | | |
| Male | 400 (55.6) | 96 (54.6) | 94 (52.8) | 98 (55.7) | 112 (59.0) |
| Female | 320 (44.4) | 80 (45.5) | 84 (47.2) | 78 (44.3) | 78 (41.1) |
| Self-reported race/ethnicity, n (%) | | | | | |
| Non-Hispanic white | 612 (85.0) | 144 (81.8) | 154 (86.5) | 146 (83.0) | 168 (88.4) |
| Black | 50 (6.9) | 12 (6.8) | 9 (5.1) | 16 (9.1) | 13 (6.8) |
| Hispanic | 15 (2.1) | 6 (3.4) | 1 (0.6) | 3 (1.7) | 5 (2.6) |
| Others[b] | 43 (6.0) | 14 (8.0) | 14 (7.9) | 11 (6.3) | 4 (2.1) |

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| **Characteristics** | **Total sample (n=720)** | **Active vitamin D3 and active omega-3s (n=176)** | **Active vitamin D3 and placebo omega-3s (n=178)** | **Placebo Vitamin D3 and active omega-3s (n=176)** | **Placebo Vitamin D3 and placebo omega-3s (n=190)** |
|---|---|---|---|---|---|
| Education, n (%) | | | | | |
| Did not complete high school | 6 (0.8) | 1 (0.6) | 1 (0.6) | 1 (0.6) | 3 (1.6) |
| High school diploma or GED | 63 (8.8) | 15 (8.5) | 11 (6.2) | 18 (10.2) | 19 (10.0) |
| Attended or graduated college | 268 (37.3) | 66 (37.5) | 62 (35.0) | 70 (39.8) | 70 (36.8) |
| Post-college | 382 (53.1) | 94 (53.4) | 103 (58.2) | 87 (49.4) | 98 (51.6) |
| Self-reported annual household income ≥$50,000, n (%) | 493 (79.3) | 122 (81.3) | 123 (79.4) | 117 (77.5) | 131 (78.9) |
| BMI, Mean (SD), $kg/m^2$ | 27.9 (5.1) | 28.1 (5.3) | 27.4 (4.8) | 28.5 (4.9) | 27.7 (5.4) |
| Total physical activity[c], MET-hours/week, median (IQR) | 21.6 (7.8 - 38.4) | 24.0 (9.7 - 45.0) | 20.5 (6.7 - 37.0) | 21.2 (8.0 - 36.7) | 22.0 (7.4 - 39.8) |
| Current smoking, n (%) | 31 (4.3) | 8 (4.6) | 7 (4.0) | 8 (4.6) | 8 (4.3) |
| Daily alcohol use, n (%) | 226 (33.3) | 52 (31.3) | 57 (33.9) | 56 (34.6) | 61 (33.5) |

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| **Characteristics** | **Total sample (n=720)** | **Active vitamin D3 and active omega-3s (n=176)** | **Active vitamin D3 and placebo omega-3s (n=178)** | **Placebo Vitamin D3 and active omega-3s (n=176)** | **Placebo Vitamin D3 and placebo omega-3s (n=190)** |
|---|---|---|---|---|---|
| Hypertension[d], n (%) | 308 (43.0) | 78 (44.3) | 68 (38.4) | 81 (46.6) | 81 (42.6) |
| Diabetes[e], n (%) | 56 (7.8) | 16 (9.1) | 15 (8.4) | 11 (6.3) | 14 (7.4) |
| High Cholesterol, n (%) | 262 (36.4) | 74 (42.1) | 62 (35.0) | 59 (33.5) | 67 (35.3) |
| Current use of supplemental vitamin D[f], n (%) | 329 (45.7) | 72 (40.9) | 83 (46.6) | 85 (48.3) | 89 (46.8) |
| Total fish and seafood[g], n (%) for median <1.93 servings/week | 340 (50.2) | 83 (50.3) | 77 (45.6) | 83 (51.6) | 97 (53.3) |
| *Blood biomarker levels* | | | | | |
| 25(OH)D levels,[h] mean (SD) | 28.2 (8.8) | 27.5 (8.6) | 27.8 (8.6) | 29.0 (9.7) | 28.5 (8.1) |
| EPA levels,[i] mean (SD) | 0.7 (0.4) | 0.7 (0.4) | 0.8 (0.4) | 0.8 (0.4) | 0.7 (0.4) |
| DHA levels,[i] mean (SD) | 2.2 (0.7) | 2.2 (0.7) | 2.2 (0.7) | 2.2 (0.7) | 2.3 (0.7) |

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| **Characteristics** | **Total sample (n=720)** | **Active vitamin D3 and active omega-3s (n=176)** | **Active vitamin D3 and placebo omega-3s (n=178)** | **Placebo Vitamin D3 and active omega-3s (n=176)** | **Placebo Vitamin D3 and placebo omega-3s (n=190)** |
|---|---|---|---|---|---|
| PF-10 score[j] categories, n (%) | | | | | |
| 0-25 points | 4 (0.6) | 1 (0.6) | 3 (1.8) | 0 (0.0) | 0 (0.0) |
| 25-50 points | 8 (1.2) | 0 (0.0) | 2 (1.2) | 3 (1.9) | 3 (1.7) |
| 50-75 points | 32 (4.7) | 11 (6.7) | 6 (3.6) | 8 (4.9) | 7 (3.9) |
| 75+ points | 634 (93.5) | 153 (92.7) | 158 (93.5) | 151 (93.2) | 172 (94.5) |
| *Neuropsychiatric and Cognitive measures* | | | | | |
| PHQ-9 score, median (range) | 0.0 (0.0 - 9.0) | 1.0 (0.0 - 5.0) | 1.0 (0.0 - 9.0) | 0.0 (0.0 - 9.0) | 0.0 (0.0 - 8.0) |
| PHQ-9 score categories, n (%) | | | | | |
| None/minimal depression (0-4 points) | 692 (96.1) | 171 (97.2) | 167 (93.8) | 168 (95.5) | 186 (97.9) |
| Mild depression (5-9 points) | 28 (3.9) | 5 (2.8) | 11 (6.2) | 8 (4.6) | 4 (2.1) |

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| Characteristics | Total sample (n=720) | Active vitamin D3 and active omega-3s (n=176) | Active vitamin D3 and placebo omega-3s (n=178) | Placebo Vitamin D3 and active omega-3s (n=176) | Placebo Vitamin D3 and placebo omega-3s (n=190) |
|---|---|---|---|---|---|
| GAD-7 score, median (range) | 0.0 (0.0 - 14.0) | 0.0 (0.0 - 10.0) | 0.0 (0.0 - 14.0) | 0.0 (0.0 - 8.0) | 0.0 (0.0 - 13.0) |
| None/minimal (0-4 points) | 688 (95.7) | 170 (96.6) | 166 (93.3) | 167 (95.4) | 185 (97.4) |
| Mild (5-9 points) | 27 (3.8) | 5 (2.8) | 11 (6.2) | 8 (4.6) | 3 (1.6) |
| Moderate or higher (10+ points) | 4 (0.6) | 1 (0.6) | 1 (0.6) | 0 (0.0) | 2 (1.1) |
| DSM-IV anxiety disorders,[k] n (%) | 24 (3.3) | 8 (4.6) | 3 (1.7) | 4 (2.3) | 9 (4.7) |
| DSSI score, median (range) | 31.0 (17.0 - 33.0) | 31.0 (17.0 - 33.0) | 30.0 (21.0 - 33.0) | 31.0 (19.0 - 33.0) | 31.0 (20.0 - 33.0) |
| AUDIT-C score, median (range) | 3.0 (0.0 - 10.0) | 3.0 (0.0 - 7.0) | 3.0 (0.0 - 10.0) | 3.0 (0.0 - 10.0) | 3.0 (0.0 - 9.0) |
| AUDIT-C score categories, n (%) | | | | | |
| 0-4 points | 604 (83.9) | 150 (85.2) | 150 (84.3) | 144 (81.8) | 160 (84.2) |
| 5+ points | 116 (16.1) | 26 (14.8) | 28 (15.8) | 32 (18.2) | 30 (15.8) |
| Caregiving for relative, friend or loved one, n (%) | 96 (13.4) | 17 (9.7) | 28 (15.8) | 26 (14.8) | 25 (13.3) |

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| Characteristics | Total sample (n=720) | Active vitamin D3 and active omega-3s (n=176) | Active vitamin D3 and placebo omega-3s (n=178) | Placebo Vitamin D3 and active omega-3s (n=176) | Placebo Vitamin D3 and placebo omega-3s (n=190) |
|---|---|---|---|---|---|
| Zarit burden score,[l] median (range) | 7.0 (0.0 - 25.0) | 6.0 (0.0 - 21.0) | 8.0 (0.0 - 24.0) | 9.0 (0.0 - 25.0) | 6.0 (0.0 - 19.0) |
| 3MS score, median (range) | 96.0 (78.0 - 100.0) | 96.0 (80.0 - 100.0) | 97.0 (81.0 - 100.0) | 95.0 (80.0 - 100.0) | 96.0 (78.0 - 100.0) |

Abbreviation: SD, standard deviation; BMI, body mass index; MET, metabolic equivalent of task; PF, physical function; 25(OH)D, 25-hydroxyvitamin D; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; SPPB, Short Physical Performance Battery; TUG, Timed Up and Go; PHQ, Patient Health Questionnaire; GAD, Generalized anxiety disorder; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; DSSI, Duke Social Support Index; AUDIT-C, Alcohol Use Disorders Identification Test-Concise; 3MS, The Modified Mini-Mental State Exam.

[a] Figures for percentages may not add to 100.0 due to rounding.

[b] Others includes Asian, Native American/Alaska Native, Native Hawaiian or other Pacific Islander, multiple race, or unknown race and/or unknown ethnicity.

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[c] Leisure-time physical activities: walking or hiking; jogging; running; bicycling; aerobic exercise/aerobic dance/exercise machines; lower intensity exercise/yoga/stretching/toning; tennis/squash/ racquetball; lap swimming; weightlifting/strength training; other exercise.

[d] Hypertension: Ever diagnosed with high blood pressure or ever use of anti-hypertensive medication.

[e] Diabetes: Ever diagnosed with diabetes or current use of anti-diabetic medication.

[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] Includes dark-meat fish (e.g., mackerel, salmon, sardines, bluefish, swordfish, canned tuna) and other fish and seafood (e.g., cod, haddock, halibut, breaded fish cakes, pieces, or fish sticks, shrimp, lobster, scallops).

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

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

[l] PF-10 of the Short-Form-36 (SF-36) was administered to assess physical/functional limitation;[20] higher score denotes higher physical function.

[k] DSM-IV anxiety disorders included agoraphobia, GAD, panic disorders (current, past, and lifetime limited panic attacks), social phobia (generalized and non-generalized).

[l] Zarit burden score was computed among those who reported regularly providing caregiving or assistance to relative, friend or other loved one.

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**Supplementary Table 3. Effect of vitamin D3 on risk of a composite depression outcome in risk group of selective prevention.**

| **Composite depression outcome**[a] | **Vitamin D3 group** | | **Placebo group** | | RR (95% CI)[c] | P-interaction[d] |
|---|---|---|---|---|---|---|
| | Event/no. of participants | Case rate/100 persons | Event/no. of participants | Case rate/100 persons | | |
| *≥1 high-risk factors for late-life depression* | | | | | | 0.23 |
| Yes (n=438)[b] | 15/197 | 7.6 | 16/201 | 8.0 | 0.96 (0.47 to 1.92) | |
| No (n=282) | 7/125 | 5.6 | 10/139 | 7.2 | 0.78 (0.27 to 2.04) | |

Abbreviation: MDD, major depressive disorder; RR, relative risk; CI, confidence interval; PHQ, patient health questionnaire

[a] The composite depression outcome was defined as incident DSM-IV MDD diagnosis and/or PHQ-9≥10 at 2-year CTSC follow-up, or incident depression in the main VITAL cohort during the 2-year CTSC follow-up period. From a total 720 eligible participants, 662 completed follow-up at year 2.

[b] Selective prevention targeted participants with ≥1 high-risk factors for late-life depression at baseline; see details in Supplementary Appendix 1 (under E. Approach for selective prevention).

[c] Relative risk and CI were based on exact tests using the exact chi-square score statistic.

[d] P-interaction was calculated using the Zelen exact test for equal odds ratios. The Zelen exact test was performed to determine whether effects of vitamin D3, compared to placebo, differ across risk group of selective prevention.

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**Supplementary Table 4. Effect of omega-3s on risk of a composite depression outcome in risk group of selective prevention.**

| Composite depression outcome[a] | Omega-3s group | | Placebo group | | RR (95% CI)[c] | P-interaction[d] |
|---|---|---|---|---|---|---|
| | Event/no. of participants | Case rate/100 persons | Event/no. of participants | Case rate/100 persons | | |
| *≥1 high-risk factors for late-life depression* | | | | | | 0.12 |
| Yes (n=438)[b] | 14/201 | 7.0 | 17/197 | 8.6 | 0.81 (0.37 to 1.66) | |
| No (n=282) | 10/123 | 8.1 | 7/141 | 5.0 | 1.64 (0.63 to 4.65) | |

Abbreviation: MDD, major depressive disorder; RR, relative risk; CI, confidence interval; PHQ, patient health questionnaire

[a] The composite depression outcome was defined as incident DSM-IV MDD diagnosis and/or PHQ-9≥10 at 2-year CTSC follow-up, or incident depression in the main VITAL cohort during the 2-year CTSC follow-up period. From a total 720 eligible participants, 662 completed follow-up at year 2.

[b] Selective prevention targeted participants with ≥1 high-risk factors for late-life depression at baseline; see details in Supplementary Appendix 1 (under E. Approach for selective prevention).

[c] Relative risk and CI were based on exact tests using the exact chi-square score statistic.

[d] P-interaction was calculated using the Zelen exact test for equal odds ratios. The Zelen exact test was performed to determine whether effects of omega-3s, compared to placebo, differ across risk group of selective prevention.

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**Supplementary Table 5. Effect of each of treatment agent on risk of incident DSM-IV MDD in the total sample (n=720).**

**A) Vitamin D3 vs. placebo**

| DSM-IV incident MDD | Vitamin D3 group | | Placebo group | | RR (95% CI)[a] | P-value[b] |
|---|---|---|---|---|---|---|
| | Event/no. of participants | Case rate/100 persons | Event/no. of participants | Case rate/100 persons | | |
| Total sample (n=720) | 13/322 | 4.0 | 21/340 | 6.2 | 0.65 (0.32 to 1.29) | 0.22 |

**B) Omega-3s vs. placebo**

| DSM-IV incident MDD | Omega-3s group | | Placebo group | | RR (95% CI)[a] | P-value[b] |
|---|---|---|---|---|---|---|
| | Event/no. of participants | Case rate/100 persons | Event/no. of participants | Case rate/100 persons | | |
| Total sample (n=720) | 19/324 | 5.9 | 15/338 | 4.4 | 1.32 (0.67 to 2.83) | 0.48 |

Abbreviation: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; MDD, major depressive disorder; RR, relative risk; CI, confidence interval

[a] Relative risk and CI were based on exact tests using the exact chi-square score statistic.

[b] Fisher exact test was used to determine if the proportions of categories in two group variables significantly differ from each other; exact p-value was reported. From a total 720 eligible participants, 662 completed follow-up at year 2.

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**Supplementary Table 6. Adjusted mean difference in 2-year change since baseline in PHQ-9 score comparing treatment and placebo groups in the total sample (n=720).**

| | No. of eligible participants | Vitamin D3 vs. placebo | | Omega-3s vs. placebo | |
|---|---|---|---|---|---|
| | | Mean difference (95% CI)[a] | p-value | Mean difference (95% CI)[b] | p-value |
| Total sample | 720 | -0.08 (-0.30 to 0.13) | 0.44 | 0.20 (-0.02 to 0.41) | 0.07 |

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

[a] Models were controlled for age, sex, and marine omega-3 fatty acids randomization group.

[b] Models were controlled for age, sex, and vitamin D3 randomization group.

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**Supplementary Table 7. Spearman correlations between subjective physical function and objective physical performance scores.**

| Tests | | PF-10 score (n=678) | SPPB score (n=538) | TUG score (n=461) |
|---|---|---|---|---|
| PF-10 score (n=678) | rho | -- | 0.36 | -0.36 |
| | p-value | | <0.001 | <0.001 |
| SPPB score (n=538) | rho | 0.36 | -- | -0.58 |
| | p-value | <0.001 | | <0.001 |
| TUG score (n=461) | rho | -0.36 | -0.58 | -- |
| | p-value | <0.001 | <0.001 | |

Abbreviation: PF-10, 10-item physical function scale from the Medical Outcomes Study Short-Form 36 (SF-36);[20] SPPB, Short Physical Performance Battery;[38] TUG, The Timed Up and Go test.[39]

The SPPB and TUG are objective physical performance measures and were used to assess lower extremity function. The Spearman correlations were used to assess the validity of self-reported physical function via comparisons with objective physical performance tests. We have provided more details in Supplementary Appendix 1 (See under F. Objective physical performance measures; G. Validity checks for subjective physical function).

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**Supplementary Table 8. Mean (SD) of SPPB score according to items on the PF-10 scale.**

| PF-10 scale | Mean (SD) of SPPB score | | p-value[b] |
|---|---|---|---|
| | Normal PF[a] | Low PF[a] | |
| Health limit your ability for vigorous activities? | 9.8 (1.0) | 9.1 (1.6) | <0.01 |
| Health limit your ability for moderate activities? | 9.6 (1.2) | 8.2 (1.8) | <0.01 |
| Health limit your ability for carrying groceries? | 9.6 (1.2) | 7.8 (1.9) | <0.01 |
| Health limit your ability for climbing several flights? | 9.7 (1.2) | 8.6 (1.8) | <0.01 |
| Health limit your ability for climbing one flight of stairs? | 9.6 (1.2) | 7.5 (1.9) | <0.01 |
| Health limit your ability for bending, kneeling, and stooping? | 9.7 (1.1) | 8.8 (1.7) | <0.01 |
| Health limit your ability for walking more than 1 mile? | 9.7 (1.1) | 8.3 (2.0) | <0.01 |
| Health limit your ability for walking several blocks? | 9.6 (1.2) | 8.2 (1.9) | <0.01 |
| Health limit your ability for walking one block? | 9.6 (1.3) | 7.7 (1.9) | <0.01 |
| Health limit your ability for bathing or dressing? | 9.6 (1.3) | 8.0 (2.0) | <0.01 |

Abbreviation: PF-10, 10-item physical function from the Medical Outcomes Study Short-Form 36 (SF-36);[20] SPPB, Short physical performance battery;[38] SD, standard deviation.

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[a] Individuals were classified as having adequate/normal PF or low PF for a given item based on their questionnaire responses; endorsement of ‘yes, limited a little’ or ‘yes, limited a lot’ was categorized as low PF.

[b] P-values were based on Wilcoxon two-sample test.

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**Supplementary Figure 1. Diagram showing number of participants identified for indicated and selective prevention strategies for late-life depression.**

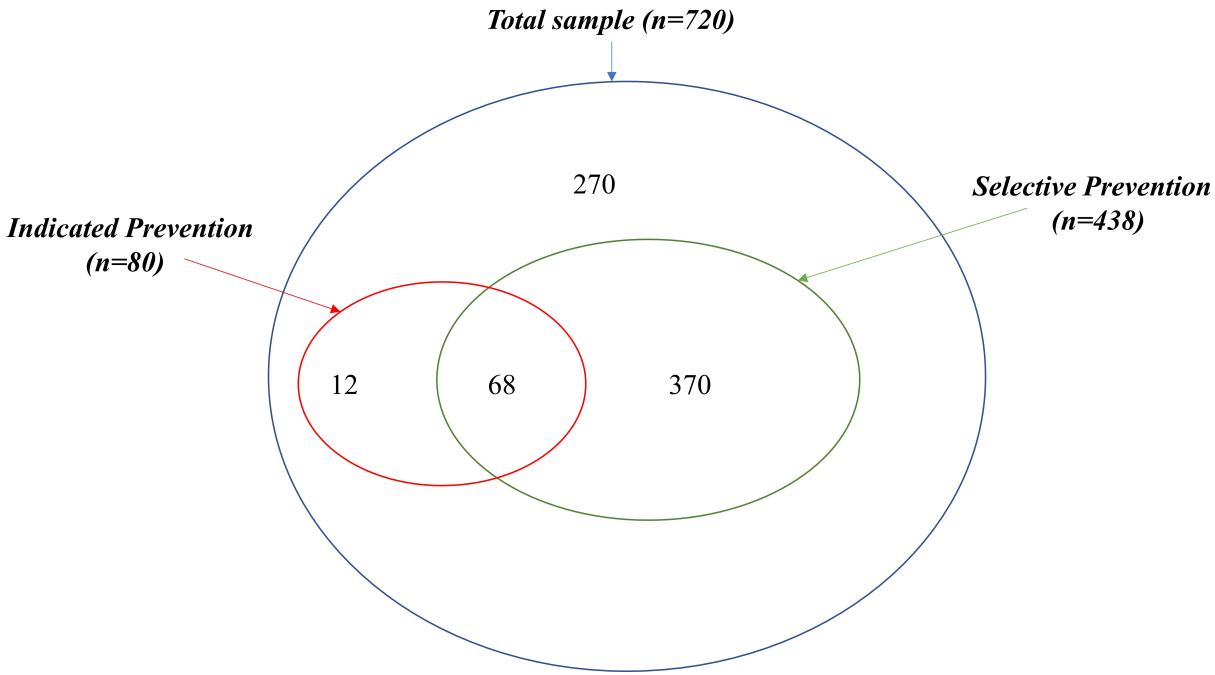


Figure depicts all participants in the study. Of those able to be targeted for indicated prevention (i.e., who had subthreshold depression at baseline), 85.0% (n=68/80) also had ≥1 high-risk factors for late-life depression (i.e., able to be targeted for selective prevention).

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