Effects of Vitamin D_3 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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ABSTRACT

Objective: To test vitamin D_3 and omega-3 fatty acids (omega-3s) for late-life depression prevention under the National Academy of Medicine framework for indicated (targeting subthreshold depression) and selective (targeting presence of high-risk factors) prevention.

Methods: The VITamin D and OmegA-3 TriaL (VITAL) is a 2×2 factorial trial of vitamin D_3 (2,000 IU/d) and/or omega-3s (1 g/d) for cardiovascular and cancer prevention (enrollment: November 2011–March 2014; end date: December 31, 2017). In this targeted prevention study, we included 720 VITAL clinical sub-cohort participants who completed neurobehavioral assessments at baseline and 2 years (91.9% retention). High-risk factors were subthreshold or clinical anxiety, impaired activities of daily living, physical/functional limitation, medical comorbidity, cognitive impairment, caregiving burden, problem drinking, and low psychosocial support. Coprimary outcomes were incident major depressive disorder (MDD), adjudicated using *DSM-IV* (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition), and change in mood (Patient Health Questionnaire-9 [PHQ-9]). We used exact tests to determine treatment effects on MDD incidence and repeated-measures models to determine treatment effects on PHQ-9.

Results: A total of 11.1% had subthreshold depression, 60.8% had ≥ 1 high-risk factor, MDD incidence was 4.7% (5.1% among completers), and mean PHQ-9 score change was 0.02 points. Among those with subthreshold depression, the MDD risk ratio (95% confidence interval) was 0.36 (0.06 to 1.28) for vitamin D_3 and 0.85 (0.25 to 2.92) for omega-3s, compared to placebo; results were also null among those with ≥ 1 high-risk factor (vitamin D_3 vs placebo: 0.63 [0.25 to 1.53]; omega-3s vs placebo: 1.08 [0.46 to 2.71]). There were no significant differences in PHQ-9 score change comparing either supplement with placebo.

Conclusions: Neither vitamin D_3 nor omega-3s showed benefits for indicated and selective prevention of late-life depression; statistical power was limited.

Trial Registration: ClinicalTrials.gov identifier: NCT01696435

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Late-life depression (LLD) prevention can be efficiently accomplished by employing the National Academy of Medicine (NAM) framework for prevention of mental disorders; ie, targeting those with subthreshold depression (indicated prevention) or high-risk factors (selective prevention).[1] Compared to traditional prevention frameworks (ie, primary, secondary, and tertiary prevention), the NAM framework has high clinical utility in LLD prevention: it defines at-risk populations using evidence-based knowledge of contextual factors and involves targeted interventions among those at highest risk. Presence of subthreshold depression and presence of selective high-risk factors are responsible for 25% and 50%, respectively, of all incident major depressive disorder (MDD) cases occurring during late life.[2–4]

Older adults with subthreshold depressive symptoms and LLD high-risk factors (eg, medical comorbidity, caregiving strain, low social support) may also have elevated inflammation levels or poor vascular and metabolic health.[5,6] Several lines of evidence suggest that vitamin D_3 and omega-3 fatty acids (omega-3s) promote mood health by decreasing inflammation and improving metabolic indicators, and also via neuroprotective benefits[7–10]; if applied among targeted groups who constitute a relatively large proportion of cases, these supplements might offer substantial benefits for LLD prevention. Prior randomized controlled trials (RCTs) of indicated and selective LLD prevention have largely applied psychological interventions; MDD relative risk reductions of up to ~50%–60% were observed.[11–14] Vitamin D_3 and omega-3 supplements may offer additional advantages for targeted LLD prevention, as they are safe, inexpensive, easily accessible, and highly acceptable to most people due to their simplicity.[15]

Over the last two decades, only 4 RCTs[16–19] examined the effects of vitamin D_3 supplementation of ≥ 12 months' duration for indicated and selective prevention of depression in mid- and/or late-life adults; 3 trials showed no benefit of vitamin D_3 for MDD risk or mood among those with subthreshold depression and/or ≥ 1 high-risk factor.[16–18] Regarding omega-3s, only 4 RCTs[17,20–22] examined effects

Clinical Points

- Limited trial evidence exists on whether supplementations of vitamin D_3 (2,000 IU/d) and/or marine omega-3 fatty acids (1 g/d) are beneficial for prevention of late-life depression among those at higher risk (ie, those with subthreshold depression or with ≥ 1 high-risk factor for depression).
- Daily supplementation of vitamin D_3 and marine omega-3 fatty acids did not show an advantage over placebo among at-risk participants for late-life depression.

of supplementation of ≥ 12 months' duration for indicated and selective prevention of depression in mid- and/or late-life adults; no benefits on MDD were found. Most prior RCTs of nutrient interventions used a single risk factor for addressing selective prevention of MDD (eg, physical/functional impairment or medical comorbidity). Yet, the combination of several selective risk factors appears responsible for the majority of LLD cases.[2,3,23] While substantial benefits might be achieved using nutrient supplements for targeted LLD prevention, data from RCTs using such approaches are limited.

VITAL-DEP (VITamin D and OmegA-3 TriaL-Depression Endpoint Prevention; ClinicalTrials.gov identifier: NCT01696435), an ancillary study to VITAL, addressed these knowledge gaps by testing vitamin D_3 or omega-3s supplementation for indicated and selective prevention of LLD in a deeply phenotyped sub-cohort of 720 participants who completed repeat in-clinic assessments. In this targeted RCT, we hypothesized that daily supplementation with vitamin D_3 or omega-3s, compared to placebos, would show benefits for indicated and selective prevention of LLD over a 2-year follow-up.

METHODS

Trial Design

VITAL randomized 25,871 participants (men aged ≥ 50 and women aged ≥ 55 years) to receive vitamin D_3 (2,000 IU/d), omega-3s (1 g/d including 465 mg eicosapentaenoic acid [EPA] and 375 mg docosahexaenoic acid [DHA]) and/or matching placebos in a 2 × 2 factorial design for prevention of cardiovascular disease and cancer (enrollment period: November 2011–March 2014; end of the intervention: December 31, 2017); the protocol was published elsewhere.[24] VITAL used a pragmatic, hybrid design that included a nationwide cohort of 25,871 participants and a sub-cohort of 1,054 participants who lived near an affiliated National Institutes of Health (NIH)–sponsored Harvard Catalyst–Clinical Translational Science Center (CTSC) in Boston, Massachusetts, and presented at the CTSC Center for Clinical Investigation for detailed, in-person assessments at baseline and 2 years. All VITAL-CTSC participants were invited to take part in the 45-minute VITAL-DEP neuropsychiatric assessment.[25] Participants were eligible for this study if they did not have (1) any of these psychiatric disorders, as determined by the Mini-International Neuropsychiatric Interview (MINI) for the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*)[26]: current depression (MDD or major depressive episode), alcohol or substance abuse/dependence in the past 12 months, primary psychotic disorders (eg, schizophrenia) or psychotic mood disorders, bipolar disorder, obsessive-compulsive disorder, or posttraumatic stress disorder; (2) unstable psychiatric symptoms during evaluation (eg, suicidality, psychosis); or (3) dementia-level cognitive impairment determined by norm-based cut-points.[27,28] All participants provided written informed consent, and study approvals were obtained from the Institutional Review Board of Mass General Brigham.

This article addresses a secondary aim of the VITAL-DEP study protocol.[25] VITAL and VITAL-DEP were designed on the basis of an a priori assumption of no interaction between agents, and the prespecified primary analyses examined separately the main effects of each agent. However, the 2 × 2 factorial design of the study allowed for exploratory analyses addressing potential interaction; results for the interaction between treatment agents were reported in subgroup analyses elsewhere, and there was no evidence of interaction between agents.[29,30]

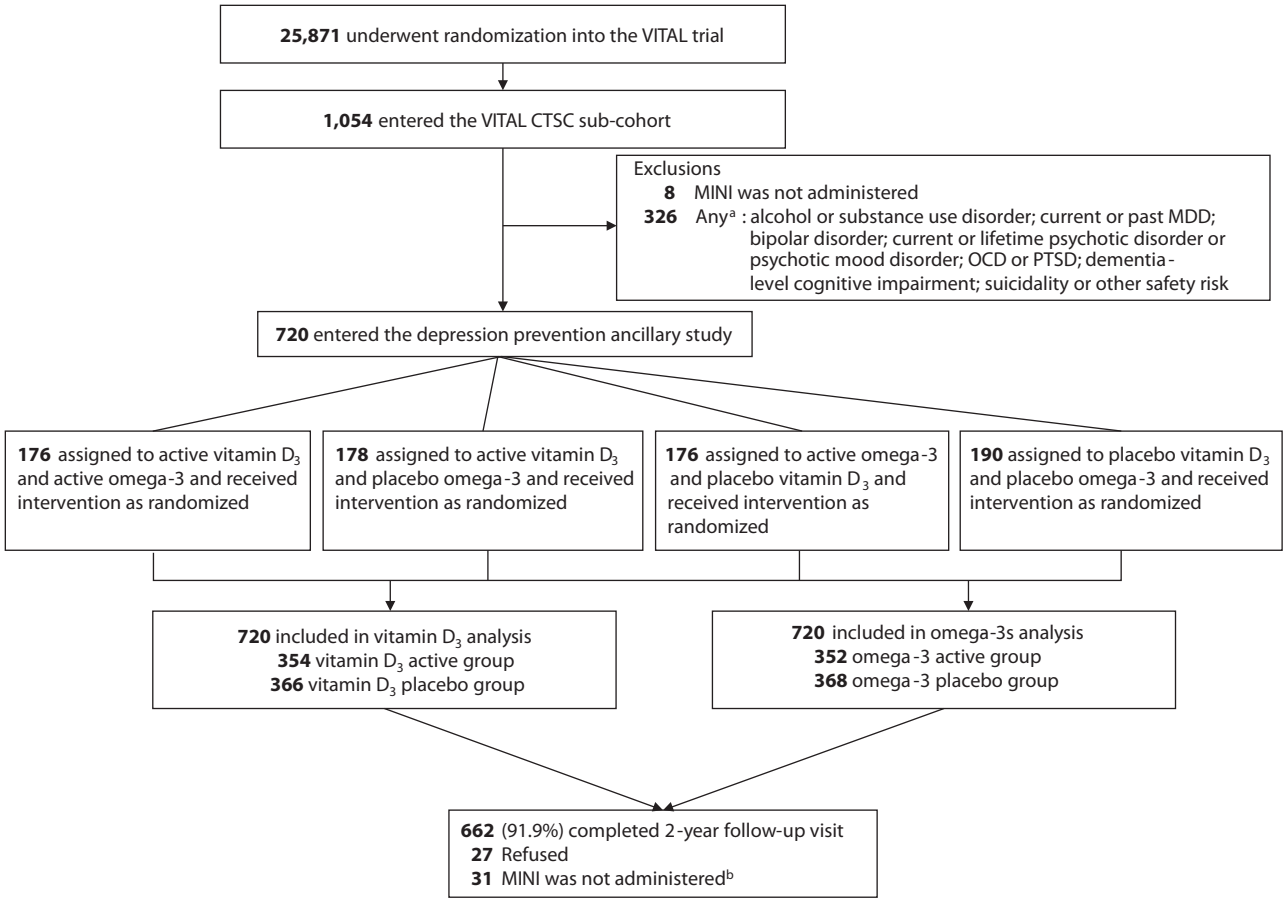
Procedures

Per the study protocol,[25] baseline assessment was used to identify participants eligible for follow-up for MDD at 2 years and to determine at-risk groups for indicated and selective prevention. The MINI was used to achieve valid, time-efficient determinations of eligibility and MDD outcomes.[26] Study psychiatrists immediately evaluated participants presenting with unstable psychiatric symptoms (eg, suicidality, manic symptoms, psychosis) to determine their safety and ability to participate; see Supplementary Appendix 1 for details.

Indicated Prevention

We identified participants with subthreshold depression—ie, clinically meaningful depressive symptoms without meeting *DSM-IV* criteria for MDD or dysthymia on the MINI—by leveraging both detailed neurobehavioral data from baseline CTSC visits and concurrent self-reported depression measures in the VITAL baseline questionnaires. Subthreshold depression was defined by the presence of any of the following[31,32]: (1) Patient Health Questionnaire-9 (PHQ-9)[33] score or PHQ-8[34] score between 5 and 9 points; (2) core features of depression (anhedonia and/or dysphoria) present at least "more than half the days" for ≥ 2 weeks in the past 2 years; (3) subsyndromal depression including minor depression on the MINI (at least 2 but fewer than 5 depression module symptoms) or the PHQ (at least 2 but fewer than 5 symptoms present at least "more than half the days" for ≥ 2 weeks); or (4) dysthymic symptoms, defined as self-report of depressed mood most of the time for ≥ 2 consecutive years, with symptoms active in the past 1 year.

Figure 1. Randomization and Follow-Up of Participants



[a]Participants could have had more than one exclusion condition.
[b]Follow-up MINI assessments were not administered due to lost to follow-up, refusal of the MINI assessment at the follow-up CTSC visit, or study withdrawal.
Abbreviations: CTSC = Clinical and Translational Science Center, MDD = major depressive disorder, MINI = Mini-International Neuropsychiatric Interview,[26] OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder, VITAL = VITamin D and OmegA-3 TriaL.[24]

Selective Prevention

We determined participants with ≥ 1 high-risk factor by leveraging robust literature on LLD risk architecture.[2,3,23] We used detailed mood, neuropsychiatric, and well-being measures in the CTSC and self-reported physical and health measures on VITAL baseline questionnaires to classify high-risk participants; see Supplementary Appendix 1 for descriptions of measures. High-risk factors were subthreshold anxiety (Generalized Anxiety Disorder-2 [GAD-2] score ≥ 3 or GAD-7 score ≥ 5)[35,36] or clinical anxiety (*DSM-IV* anxiety disorders); impaired activities of daily living (instrumental activities of daily living [IADL] score ≥ 1)[37]; problem/hazardous drinking (Alcohol Use Disorders Identification Test-Concise [AUDIT-C] score ≥ 5)[38]; physical/functional limitation (determined using the 10-item Physical Functioning scale [PF-10] from the Medical Outcomes Short Form-36)[39]; medical comorbidity (≥ 1 chronic disease); cognitive impairment (below Modified Mini-Mental State Exam [3MS][40] norm-based cutoff scores that factored age, sex, education, race and ethnicity)[41]: < 92 among non-Hispanic White men, < 95 among non-Hispanic White women, < 89 among Black and Hispanic participants, < 91 among participants with other race or ethnicity); caregiving burden (Zarit brief burden interview score ≥ 10)[42]; and low psychosocial support (Duke Social Support Index [DSSI][43,44] score ≤ 26).

Coprimary Outcomes

The two coprimary outcomes were (1) risk of incident MDD and (2) 2-year change in mood score. Incident MDD was defined per *DSM-IV* criteria using the MINI at 2 years. The PHQ-9 was used to ascertain mood score at baseline and 2 years (higher scores indicate worse mood; range, 0–27 points); the minimal clinically important difference (MCID) for change in PHQ-9 score was 0.5 points.

Secondary Outcome

We addressed a composite incident depression outcome that leveraged both in-person CTSC diagnoses and, as previously described,[25] depression outcomes ascertained from main VITAL study questionnaires. This outcome, used for a secondary analysis of selective prevention, included

DSM-IV MDD, PHQ-9 score ≥ 10, and incident case of depression in the main VITAL study within the 2-year CTSC follow-up period.[30]

Statistical Analyses

Analyses of coprimary outcomes. Prior RCTs showed ~50%–60% relative risk (RR) reductions (ie, an RR of 0.4–0.5) using indicated and selective prevention strategies.[11–13] Power calculations were based on an expected N of 855 and 2-year absolute risk of MDD of 35% among those with subthreshold depression and 25% among those with ≥ 1 high-risk factor. Based on these estimates, power was ≥ 80% to detect RRs of ≤ 0.60 and ≤ 0.50, respectively, for indicated and selective LLD prevention. Regarding 2-year change in PHQ-9 score, power was 90% and > 99% to detect the MCID in risk groups of indicated and selective prevention, respectively. Analysis of treatment effects among the 720 eligible participants in this study was based on intention-to-treat. Differences between the original statistical analysis plan and current procedures are detailed in Supplementary Appendix 1.

Participants' characteristics were compared across the 4 treatment groups (vitamin D_3, omega-3s, both agents, or both placebos). We used χ^2 statistics to determine effects of treatment agents versus placebos on risk of incident MDD among those with versus without subthreshold depression or with versus without high-risk factors for depression; RR and exact 95% confidence intervals (CIs) are reported. The Zelen exact test was used as an interaction test to determine whether treatment effects on incident MDD differed across risk groups of indicated and selective prevention.

In examining 2-year change in mood score, general linear models of response profiles were used to estimate the means and were adjusted for age, sex, and concurrent randomized agent, and time was modeled as an indicator variable; missing outcome data were assumed to be missing at random.[45] The mean difference between treatment versus placebo groups in change in PHQ-9 score was estimated using a time × treatment interaction. Models were fitted using maximum likelihood, correlations within participants were modeled using an unstructured covariance pattern, and statistical tests used the Wald test.

Secondary analyses. Exact χ^2 statistics were used to determine effects of treatment agents, compared to placebos, on the composite depression outcome among those with versus without ≥ 1 high-risk factor; the Zelen exact test was used to determine whether treatment effects differed across risk group of selective prevention.

Non-prespecified and post hoc analyses. First, effects of treatment agents versus placebos on MDD risk and change in PHQ-9 score were estimated in the full sample of 720 participants, rather than separately by indicated and selective prevention risk group. Second, as physical/functional limitation is one of the largest single contributors to LLD risk,[2,3,23] we performed additional validation checks for the self-reported PF-10 (available in 94% of sample) by comparing it to the concurrent gold-standard objective physical performance tests (available in a smaller subset of the sample [n ~500]) (see Supplementary Appendix 1).

Statistical analyses were performed using SAS 9.4 (SAS Institute; Cary, NC). Tests were 2-sided; for an α level of .05 with two coprimary outcomes, $P < .025$ was used for statistical significance for each outcome after Bonferroni correction. Results regarding secondary, non-prespecified, and post hoc analyses should be interpreted with caution.

RESULTS

Figure 1 summarizes the recruitment and disposition of participants. Among eligible 720 participants, 58 (8.1%) were lost to-follow-up, refused follow-up MINI assessment, or withdrew from the study; 662 (91.9%) completed MINI assessments at 2 years.

In VITAL, participants answered study pill adherence questions at 6 months and 1 year post-randomization and annually thereafter. At 2-year follow-up, the percentages of participants who reported taking at least two-thirds of study capsules were 95.4% and 94.4%, respectively, in vitamin D_3 and placebo groups and 95.0% and 95.3%, respectively, in omega-3s and placebo groups (Supplementary Table 1). The mean (SD) age of participants was 65.4 (6.5) years; 44.4% were female, and 15% were racial and/or ethnic minorities. Characteristics were balanced across randomization groups (Table 1). Of the 720 participants, there were 80 (11.1%) with subthreshold depression and 438 (60.8%) with ≥ 1 high-risk factor. Among those with subthreshold depression, presence of high-risk factors for LLD was common (Supplementary Figure 1). High-risk factors were balanced across randomization groups, except for slightly higher prevalence of cognitive impairment and physical/functional limitation among those randomized to active omega-3s. Additional characteristics are provided in Supplementary Table 2.

Results for Primary Analyses

The *DSM-IV* MDD incidence rate was 4.7% (34/720) at 2-year follow-up; the rate was 5.1% (34/662) among study completers. The absolute risk of incident MDD was 3-fold higher in participants with versus without subthreshold depression (12.5% vs 3.8%; Fisher exact P value = .002); no such difference in absolute risk was observed among those with versus without ≥ 1 high-risk factor. The mean 2-year change in PHQ-9 score was 0.02 points.

Randomization to vitamin D_3, compared to placebo, did not affect risk of incident MDD among those with versus without subthreshold depression or those with versus without ≥ 1 high-risk factor; Zelen tests showed no differences in treatment effects across risk groups (Figure 2). Regarding indicated prevention, although the estimate was in the direction of more than a 60% reduction in MDD risk among participants with subthreshold depression randomized to vitamin D_3 versus placebo, results were not statistically significant. Regarding selective prevention, no

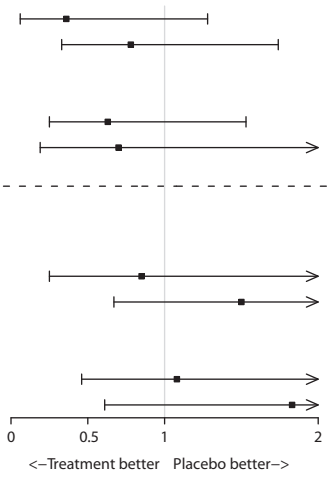
Table 1. Characteristics of Participants at Baseline, According to Randomized Assignment to Treatment Agent and/or Placebo[a]

Characteristic	Active Vitamin D_3 and Active Omega-3s (n = 176)	Active Vitamin D_3 and Placebo Omega-3s (n = 178)	Placebo Vitamin D_3 and Active Omega-3s (n = 176)	Placebo Vitamin D_3 and Placebo Omega-3s (n = 190)
Age at CTSC visit, mean (SD)	65.3 (6.3)	65.2 (6.2)	65.5 (7.0)	65.4 (6.7)
Sex				
Male	96 (54.5)	94 (52.8)	98 (55.7)	112 (58.9)
Female	80 (45.5)	84 (47.2)	78 (44.3)	78 (41.1)
Self-reported race/ethnicity				
Non-Hispanic White	144 (81.8)	154 (86.5)	146 (83.0)	168 (88.4)
Black	12 (6.8)	9 (5.1)	16 (9.1)	13 (6.8)
Hispanic	6 (3.4)	1 (0.6)	3 (1.7)	5 (2.6)
Others[b]	14 (8.0)	14 (7.9)	11 (6.3)	4 (2.1)
Subthreshold depression				
Yes[c]	20 (11.4)	22 (12.4)	22 (12.5)	16 (8.4)
No	156 (88.6)	156 (87.6)	154 (87.5)	174 (91.6)
1+ High-risk factors for late-life depression				
Yes[d]	106 (60.2)	111 (62.4)	114 (64.8)	107 (56.3)
No	70 (39.8)	67 (37.6)	62 (35.2)	83 (43.7)
Total no. of high-risk factors for late-life depression				
0	70 (39.8)	67 (37.6)	62 (35.2)	83 (43.7)
1	62 (35.2)	71 (39.9)	66 (37.5)	71 (37.4)
2	35 (19.9)	26 (14.6)	34 (19.3)	25 (13.2)
3+	9 (5.1)	14 (7.9)	14 (8.0)	11 (5.8)
Individual High-Risk Group				
Subthreshold or clinical anxiety[e]				
Yes	13 (7.4)	15 (8.4)	11 (6.3)	13 (6.9)
No	163 (92.6)	163 (91.6)	164 (93.7)	176 (93.1)
Impaired activities of daily living[f]				
Yes	7 (4.0)	3 (1.7)	7 (4.0)	4 (2.1)
No	169 (96.0)	175 (98.3)	169 (96.0)	185 (97.9)
Problem drinking[g]				
Yes	26 (14.8)	28 (15.7)	32 (18.2)	30 (15.8)
No	150 (85.2)	150 (84.3)	144 (81.8)	160 (84.2)
Physical/functional limitation[h]				
Yes	36 (21.8)	29 (17.2)	41 (25.3)	30 (16.5)
No	129 (78.2)	140 (82.8)	121 (74.7)	152 (83.5)
Medical comorbidity[i]				
Yes	23 (13.1)	25 (14.0)	22 (12.5)	23 (12.1)
No	153 (86.9)	153 (86.0)	154 (87.5)	167 (87.9)
Cognitive impairment[j]				
Yes	48 (27.4)	37 (20.9)	51 (29.0)	38 (20.1)
No	127 (72.6)	140 (79.1)	125 (71.0)	151 (79.9)
Caregiving burden[k]				
Yes	3 (1.7)	13 (7.3)	12 (6.8)	7 (3.7)
No	173 (98.3)	164 (92.7)	164 (93.2)	181 (96.3)
Low psychosocial support[l]				
Yes	5 (2.9)	15 (8.5)	10 (5.9)	9 (4.8)
No	170 (97.1)	162 (91.5)	160 (94.1)	180 (95.2)

[a]Values are shown as n (%) unless otherwise noted. Values for percentages may not add to 100.0 due to rounding.
[b]Others race/ethnicity group included Asians and Pacific Indians, American Indians, Native Hawaiian, other unknown, and missing reported race/ethnicity participants.
[c]Indicated prevention targeted participants with subthreshold depression, but who did not meet *DSM-IV* criteria for current major depressive disorders or dysthymia, at baseline.
[d]Selective prevention targeted participants with ≥ 1 high-risk factor for late-life depression at baseline; see details in Supplementary Appendix 1 (under E. Approach for selective prevention).
[e]Subthreshold or clinical anxiety was assessed based on core features of anxiety (GAD-2 score ≥ 3 or GAD-7 score ≥ 5) and/or adjudicated anxiety disorder diagnoses in administered diagnostic interviews.[36]
[f]Impaired activities in daily living was determined based on IADL score (1+ points) reported on OARS multidimensional functional assessment questionnaire.[37]
[g]Problem drinking was defined based on VITAL-DEP CTSC scoresheet alcohol gating questions and/or AUDIT-C score cutoff ≥ 5.[38]
[h]Physical/functional function limitation was assessed using the PF-10 of the SF-36.[39]
[i]Medical comorbidity was derived from the count of major chronic diseases.
[j]Cognitive impairment was determined using published 3MS (range, 0–100) norm-based cut-points, accounting for age, sex, race/ethnicity, and education, for identifying presence of cognitive impairment; for non-Hispanic White men, < 92; for non-Hispanic White women, < 95; for Black and Hispanic participants, < 89; and for Other race/ethnicity participants, < 91.[41]
[k]Caregiving burden was assessed using Zarit Burden Interview scale[42]; a cutoff of ≥ 10 and/or self-reported rating of moderately or higher caregiving burden were used to define presence of caregiving burden. The denominator for this group included participants who either did not report caregiver burden or were not providing any information on ill-caregiving.
[l]Psychosocial support was measured using 10-item DSSI[43]; a cutoff of ≤ 26 for DSSI score was used to define low psychosocial support.[44]
Abbreviations: 3MS = Modified Mini-Mental State Exam, AUDIT-C = Alcohol Use Disorders Identification Test-Concise, CTSC = Clinical Translational Science Center, DSSI = Duke Social Support Index, GAD = generalized anxiety disorder, IADL = instrumental activities of daily living, OARS = Older Americans Resources and Services, PF-10 = 10-item physical functioning scale, SF-36 = Short Form-36, VITAL-DEP = VITamin D and OmegA-3 TriaL Depression Endpoint Prevention.

Figure 2. Effect of Vitamin D3 or Omega-3s, Compared to Their Matching Placebos, on Risk of *DSM-IV* Incident MDD at 2 Years by Risk Group of Indicated and Selective Prevention[a]

	Treatment group		Placebo group			
	Event/no. of participants	Case rate per 100 persons	Event/no. of participants	Case rate per 100 persons	Relative risk[b] (95% CI)	*P*-interaction
Results for vitamin D_3 vs placebo						
Subthreshold depression						.19
Yes (n = 80)[c]	3/40	7.5	7/34	20.6	0.36 (0.06 to 1.28)	
No (n = 640)	10/282	3.6	14/306	4.6	0.78 (0.33 to 1.74)	
1+ high-risk factors for late-life depression						.29
Yes (n = 438)[d]	8/197	4.1	13/201	6.5	0.63 (0.25 to 1.53)	
No (n = 282)	5/125	4.0	8/139	5.8	0.70 (0.19 to 2.07)	
Results for omega-3s vs placebo						
Subthreshold depression						.23
Yes (n = 80)[c]	5/40	12.5	5/34	14.7	0.85 (0.25 to 2.92)	
No (n = 640)	14/284	4.9	10/304	3.3	1.50 (0.67 to 3.54)	
1+ high-risk factors for late-life depression						.22
Yes (n = 438)[d]	11/201	5.5	10/197	5.1	1.08 (0.46 to 2.71)	
No (n = 282)	8/123	6.5	5/141	3.6	1.83 (0.61 to 6.64)	



[a]From a total 720 eligible participants, 662 completed follow-up at year 2. For the coprimary outcome of incident MDD, $P < .025$ was considered as threshold for overall statistical significance.
[b]Relative risk and its CI were based on exact tests using the exact χ^2 score statistic.
[c]Indicated prevention targeted participants with subthreshold depression, but who did not meet *DSM-IV* criteria for current major depressive disorders or dysthymia, at baseline.
[d]Selective prevention targeted participants with ≥ 1 high-risk factor for late-life depression at baseline; see details in Supplementary Appendix 1 (under E. Approach for selective prevention).
[e]*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 D_3 or omega-3s, compared to placebo, differ across risk groups of indicated and selective prevention.

significant effects of vitamin D_3, compared to placebo, on risk of incident MDD were observed. The mean difference in 2-year change in PHQ-9 score comparing vitamin D_3 and placebo was not statistically significant among those with versus without subthreshold depression or those with versus without ≥ 1 high-risk factor; estimates were lower than the prespecified MCID of 0.5 points (Table 2).

Randomization to omega-3s, compared to placebo, did not affect risk of incident MDD among those with versus without subthreshold depression or those with versus without ≥ 1 high-risk factor; Zelen tests showed no differences in treatment effects across risk groups (Figure 2). Regarding indicated and selective prevention, no significant effects of omega-3s, compared to placebo, on risk of incident MDD were observed. The mean difference in 2-year change in PHQ-9 comparing omega-3s and placebo was not statistically significant among those with versus without subthreshold depression (Table 3). Regarding selective prevention, there appeared to be worse mean change over 2 years in PHQ-9 score, comparing omega-3s with placebo (0.35 points; 95% CI, 0.04 to 0.66); however, the test for multiplicative interaction was nonsignificant after Bonferroni correction, indicating no differential effect of omega-3s on change in PHQ-9 score among those with versus without ≥ 1 high-risk factor; estimates were lower than the prespecified MCID of 0.5 points.

Results for Secondary Analyses

Of the 720 participants, 48 (6.7%) developed the composite depression outcome (7.3% [48/662] among study completers). Effects of vitamin D_3 or omega-3s, versus placebos, on MDD incidence did not differ across risk groups for selective prevention (Supplementary Tables 3 and 4); neither supplement showed significant effects among those with ≥ 1 high-risk factor.

Results for Non-Prespecified and Post hoc Analyses

These results showed the following: (1) Neither supplement showed significant effects on risk of *DSM-IV* incident MDD in the full sample (Supplementary Table 5); the overall adjusted mean difference in change in PHQ-9 score at 2 years was not significant, comparing vitamin D_3 or omega-3s versus placebos (Supplementary Table 6). (2) Validation of the PF-10 in our sample showed significant correlations with objective physical performance tests and significant discrimination of Short Physical Performance Battery scores among those with versus without impairment based on the PF-10 (see Supplementary Tables 7 and 8 and Supplementary Appendix 1).

DISCUSSION

In this RCT including 720 older adults at elevated risk for depression due to presence of subthreshold depression

Table 2. Adjusted Mean Difference in Change in PHQ-9 Score at 2-Year Follow-Up Comparing Vitamin D_3 and Placebo Groups by Risk Group of Indicated and Selective Prevention[a]

Risk Group	Eligible Participants, n	Vitamin D_3 vs Placebo	
		Mean Difference (95% CI)[b]	*P*-Interaction[c]
Subthreshold depression			.86
Yes[d]	80	−0.02 (−1.26 to 1.21)	
No	640	−0.11 (−0.29 to 0.08)	
1+ High-risk factors for LLD			.53
Yes[e]	438	−0.14 (−0.45 to 0.17)	
No	282	−0.01 (−0.28 to 0.25)	

[a]For this coprimary outcome, $P < .025$ was considered as threshold for statistical significance. The prespecified MCID (minimally clinically important difference) in PHQ-9 score was 0.5 points.
[b]Results are from repeated measures model; all participants contributed to the repeated measure analysis at one and/or both time points. Models were controlled for age, sex, and marine omega-3 fatty acids randomization group.
[c]*P*-interaction is from the test of the prevention category × treatment × time interaction term in the model.
[d]Indicated prevention targeted participants with subthreshold depression, but who did not meet *DSM-IV* criteria for current major depressive disorder or dysthymia, at baseline.
[e]Selective prevention targeted participants with ≥ 1 high-risk factor for LLD at baseline; see details in Supplementary Appendix 1 (under E. Approach for selective prevention).
Abbreviations: LLD = late-life depression, PHQ-9 = Patient Health Questionnaire-9.

Table 3. Adjusted Mean Difference in Change in PHQ-9 Score at 2-Year Follow-Up Comparing Omega-3s and Placebo Groups by Risk Group of Indicated and Selective Prevention[a]

Risk Group	Eligible Participants, n	Omega-3s vs Placebo	
		Mean Difference (95% CI)[b]	*P*-Interaction[c]
Subthreshold depression			.23
Yes[d]	80	0.84 (−0.36 to 2.03)	
No	640	0.11 (−0.08 to 0.30)	
1+ High-risk factors for LLD			.05
Yes[e]	438	0.35 (0.04 to 0.66)	
No	282	−0.05 (−0.31 to 0.21)	

[a]For this coprimary outcome, $P < .025$ was considered as threshold for statistical significance. The prespecified MCID (minimally clinically important difference) in PHQ-9 score was 0.5 points.
[b]Results are from repeated measures model; all participants contributed to the repeated measure analysis at one and/or both time points. Models were controlled for age, sex, and vitamin D_3 randomization group.
[c]*P*-interaction is from the test of the prevention category × treatment × time interaction term in the model.
[d]Indicated prevention targeted participants with subthreshold depression, but who did not meet *DSM-IV* criteria for current major depressive disorder or dysthymia, at baseline.
[e]Selective prevention targeted participants with ≥ 1 high-risk factor for LLD at baseline; see details in Supplementary Appendix 1 (under E. Approach for selective prevention).
Abbreviations: LLD = late-life depression, PHQ = Patient Health Questionnaire-9.

or high-risk factors for late-life depression, neither vitamin D_3 nor omega-3s, compared with placebos, significantly affected risk of incident MDD or change in mood scores at 2 years; however, statistical power was limited by low MDD case rates (~5%).

Older persons at elevated risk for depression may have higher inflammation levels and poor vascular and metabolic health.[5,6] Vitamin D_3 and omega-3s may lower LLD risk by improving inflammatory profiles and enhancing vascular and metabolic health, as well as by improving neurotrophic and neuroprotective factors.[7–10] Our null findings regarding vitamin D_3 supplementation are consistent with results from shorter-term and/or smaller-sample RCTs of vitamin D_3 ≥ 800 IU/d that showed no benefit for indicated and selective prevention.[16–18,46] For example, a prior RCT (n = 155; MDD incidence = 3.4%)[16] found no effect of 12-month supplementation of vitamin D_3 (1,200 IU/d) on MDD risk or mood scores among older adults with subthreshold depressive symptoms, physical/functional limitation, and low vitamin D_3 levels. An RCT by Bot and colleagues (n = 1,025; MDD incidence = 10%)[17] found no beneficial effects of 12-month supplementation with a multinutrient agent containing 800 IU/d of vitamin D_3 and 1.4 g/d of omega-3s (EPA:DHA = 3:1) for MDD incidence or change in mood score over 1 year among midlife adults with overweight/obesity and subthreshold depression. Our study is consistent with these findings and has a 2-year treatment duration and higher dose of vitamin D_3 (2,000 IU/d), along with high follow-up (92%) and compliance rates (95%).

Similarly, our null findings regarding omega-3s supplementation for indicated and selective prevention of LLD are consistent with most published RCTs.[17,20–22] However, Sinn and colleagues (n = 50; mean age = 73 years)[47] found that EPA and DHA supplements, compared to placebos, have been associated with lower mood scores at 6-month follow-up in older adults with mild cognitive impairment. Overall, future trials might add clarity by integrating biomarkers and genetics when classifying at-risk populations; this approach may shed light on mechanism as well as persons most likely to benefit from treatment.

Study strengths include a well-characterized sample, factorial trial design, testing two modalities of prevention using the NAM framework, rigorously adjudicated endpoints, use of well-validated measures for characterizing

risk groups, and high follow-up and adherence rates.

This study also has limitations. First, the assessment interval was 2 years; as more than 50% of MDD cases may spontaneously remit by 12 months,[48] some cases that occurred and fully remitted between assessments may not have been ascertained. Second, among those generally healthy participants, a lower-than-expected eligible sample (720 vs 855) and low case rates limited power to detect significant effects; however, observed MDD incidence was comparable to that in recent RCTs of similar community-based participants.[16,17] To mitigate risk of type II error, we secondarily addressed selective prevention using a broader composite depression outcome; however, results were unchanged. Third, evidence suggests that doses of ≥ 1.5 g/d omega-3s may be necessary for LLD prevention[49]; however, we did not test effects of high-dose omega-3s or of different balances of EPA versus DHA. Fourth, generalizability is a potential issue; the sample included generally healthy adults and only 15% racial/ethnic minority participation.

CONCLUSIONS

Among 720 older men and women at elevated risk for depression due to presence of subthreshold depression or established high-risk factors, neither vitamin D_3 nor omega-3s, compared with placebos, significantly affected risk of incident major depressive disorder or change in mood scores over a treatment duration of 2 years; however, statistical power was limited by low MDD incidence rates. Findings do not support use of supplemental vitamin D_3 or omega-3s for indicated and selective prevention of late-life depression.

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Supplementary Material: Available at Psychiatrist.com.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Jordan F. Karp, MD, at jkarp@psychiatrist.com, or Gary W. Small, MD, at gsmall@psychiatrist.com.

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

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

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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

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

[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

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

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.

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

"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;

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.

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

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>

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 (ρ)=0.36, $p<0.001$]; negative correlations for TUG (ρ= -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 (κ) = 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 [κ = 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

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] ($\rho=0.29$, $p<0.01$).

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.

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)

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)

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)

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)

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)

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.

[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.

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.

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.

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.

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.

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).

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.

[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.

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

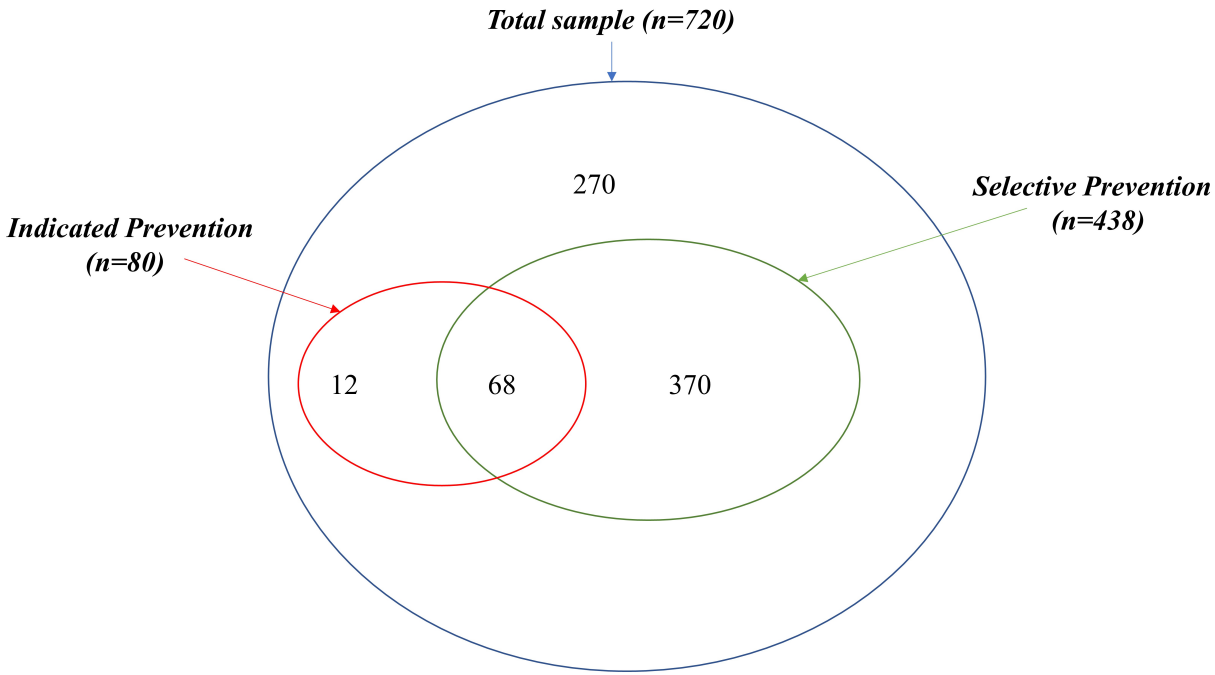

Figure depicts all participants in the study. Of those able to be targeted for indicated prevention (i.e., who had subthreshold depression at baseline), 85.0% (n=68/80) also had ≥1 high-risk factors for late-life depression (i.e., able to be targeted for selective prevention).

Supplemental References

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