Effect of cocoa extract supplementation on mental health and risk of incident late-life depression: a secondary analysis of the COSMOS trial

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A thesis

submitted in partial fulfillment of the

requirements of the degree of

MASTER OF SCIENCE

University of Washington

2023

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Program Authorized to Offer Degree:

Nutritional Sciences

University of Washington

Abstract

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Question Can cocoa extract supplementation improve subjective mental health and prevent the onset of incident late-life depression in older adults?

Findings In this secondary analysis of 21,442 adults aged 60 or older, cocoa extract supplementation did not result in a statistically significant change in subjective mental health scores compared to placebo. In 16,059 participants without a previous lifetime diagnosis of depression or receiving depression treatment (anti-depressant use or counseling within the past 2 years or regular selective serotonin reuptake inhibitor [SSRI] use), cocoa extract supplementation did not result in a reduction in incident late-life depression compared to placebo.

Meaning These findings do not support the use of cocoa extract supplementation in improving subjective mental health in older adults or as a prophylactic treatment for late-life depression.

Importance Late-life depression (LLD) has a lower remission rate, a higher recurrence rate, and is less responsive to pharmacological treatment than early-onset depression, warranting novel prophylactic and therapeutic treatments.

Objective To test the effects of cocoa extract supplementation on subjective mental health outcomes and the incidence of late-life depression in older adults.

Design, Setting, and Participants There were 21,442 men and women aged 60 years or older in the COcoa Supplement and Multivitamin Outcomes Study (COSMOS) trial, a randomized clinical trial investigating the effects of cocoa extract supplementation and a multivitamin on the primary prevention of cardiovascular disease and cancer. The intervention phase was from June 2015 to December 2020, and participants were followed for a median duration of 3.6 years. 10,723 participants were randomized to placebo and 10719 participants were randomized to cocoa extract supplementation. There were 16,059 participants at risk for incident depression.

Intervention Randomized assignment in a 2 x 2 factorial design to cocoa extract supplementation [2 capsules/d containing 500 mg cocoa flavanols] and multivitamin or placebo.

Main Outcomes and Measures The primary outcomes were mean Mental Health Inventory 5 (MHI-5) scores after 1 year and risk of incident late-life depression.

Results Cocoa extract supplementation did not result in a significant difference in MHI-5 scores at 1 year in older adults (β = -0.21, 95% CI: -0.50, 0.09). No interactions between cocoa extract and sex, baseline MHI5, or depression treatment were observed. Cocoa extract supplementation did not result in a significant difference in incident depression in older adults (HR = 0.92, 95% CI: 78, 1.09) (Table 3). No interactions between cocoa extract and sex, baseline MHI-5, or time since randomization were observed.

Conclusions and Relevance Among adults >60 years who were free of MI, stroke, and recently diagnosed cancer, cocoa extract was not effective in improving MHI-5 scores and reducing the risk of

incident depression. The findings do not support the use of cocoa extract in improving subjective mental health outcomes or as prophylactic treatment for late-life depression.

Introduction

Late-life depression – depression affecting older adults aged >60-65 years old – is a frequent cause of increased healthcare utilization and decreased quality of life in older adults.[1] In comparison to early-onset depression (EOD), late-life depression (LLD) – characteristically differentiated by cerebrovascular dysfunction, inflammation, and impaired executive function – has a lower remission rate, higher recurrence rate, and is less responsive to pharmacological treatment, highlighting the need for novel prophylactic and therapeutic treatments.[2]

Cocoa, made from the bean of the cocoa tree, *Theobroma cacao*, has recently gained interest for its potential cardiometabolic benefits.[3] Cocoa contains flavanols such as epicatechin and catechin as well as methylxanthines such as theobromine and caffeine which may mediate the potential health benefits attributed to cocoa. Recently, flavanol-rich cocoa products have been shown to decrease depressive-like behaviors in animal models, alter biomarkers associated with depression in human studies, attenuate the physiological effects of stress in humans, and improve self-reported mood in small clinical trials, making it a potential candidate as a prophylactic treatment for LLD.[4-11]

Cocoa flavanol beverages have been shown to increase cerebral blood flow (CBF) in the prefrontal cortex and anterior cingulate cortex (ACC) in humans, brain regions that have been shown to have reduced CBF in depressed patients in a recent meta-analysis.[12-14] Additionally, cocoa flavanols have been shown to increase levels of brain-derived neurotrophic factor (BDNF) – a neurotrophic factor involved in the survival, growth, and maintenance of neurons – in older adults, corroborating findings from animal studies.[15-17] Low levels of BDNF are associated with depression and the effects of anti-depressant drugs, transcranial magnetic stimulation (TMS), and electroconvulsive therapy (ECT) are likely partially mediated by increases in BDNF levels and/or BDNF-TrkB signaling.[18-21] Cocoa flavanols

have also been shown to improve self-reported calmness and contentedness and decrease mental fatigue in separate clinical trials conducted in healthy volunteers[10-11] Furthermore, cocoa flavanols have been shown to improve the vascular response to acute stress in young adults and decrease psychological stress-induced markers of inflammation in isolated PBMCs from healthy volunteers in small clinical trials.[8,9]

To date, no large-scale randomized clinical trial has evaluated the effects of flavanol-rich cocoa extract vs placebo on subjective mental health outcomes in older adults or on the risk of incident late-life depression. Using data from the Cocoa Supplement and Multivitamin Outcomes Study (COSMOS) trial, a 2 x2 factorial randomized trial investigating the effects of a cocoa extract supplement and a multivitamin in the reduction of CVD and cancer risk among older women and men, this secondary analysis tests our hypothesis that cocoa extract supplementation improves self-reported mental health outcomes and reduces the risk of incident late-life depression in older adults.[22,23] Given that many clinical trials on the effects of cocoa flavanols on cerebrovascular processes, as well as the sole prospective study investigating flavanols and late-life depression, have exclusively enrolled men or women, our analysis sought to assess the influence of sex on the effects of cocoa extract supplementation on subjective mental health and incident late-life depression.[8,12,24,25] Additionally, given that anti-depressants affect many of the same physiological processes as cocoa flavanols (e.g., gut microbial composition, cerebral blood flow, and neurotrophic factors), our analysis sought to assess potential synergistic effects between cocoa extract and anti-depressant use on 1-year MHI-5 scores. Lastly, given the possibility of a "ceiling effect" due to high average baseline subjective mental health outcomes, our analysis sought to assess interactions between cocoa extract and baseline MHI-5 on 1-year MHI-5 scores and incident late-life depression.

Methods

Participants

Enrolling 21,442 US adults, including 12,666 women aged ≥65 years and 8776 men aged ≥60, the parent COSMOS Trial (clinicaltrials.gov #NCT02422745) was a randomized, double-blind, placebo-

controlled, 2 x 2 factorial trial testing the effects of cocoa extract supplementation (2 capsules/d containing 500 mg cocoa flavanols; full composition details in Supplement 8) and a multivitamin supplement (Centrum Silver®; supplied by Pfizer Consumer Healthcare, now a part of GSK Consumer Healthcare) in the primary prevention of CVD and cancer. The recruitment process was conducted between June 2015 and March 2018 and included initial mailings to active Women's Health Initiative Extension study participants followed by mailings from Brigham and Women's Hospital (BWH) to participants contacted for the VITamin and OmegA-3 TriaL (VITAL). Mass mailings to US men and women and mailings to volunteers through other sources, including advertisements and word of mouth, completed the recruitment process. The overall process of recruitment and determining eligibility included (1) a brief initial screening questionnaire, (2) a baseline questionnaire and informed consent form, (3) a placebo run-in of ≥2 months, and (4) final compliance, eligibility, baseline characteristics, and food frequency questionnaires upon randomization. All COSMOS participants provided informed consent and trial activities were overseen by the Human Subjects Committee at BWH/Mass General Brigham. Full trial design and study compliance details can be found in the primary COSMOS manuscript.[22,23]

Exclusion Criteria

Exclusion criteria for the parent COSMOS trial included history of myocardial infarction (MI), stroke, and recently diagnosed cancer (except for nonmelanoma skin cancer). Participants with renal failure, dialysis or others serious conditions were excluded for safety. Additionally, participants with extreme sensitivity to caffeine were excluded from the trial. Participants agreed to forgo cocoa extract and multivitamin supplementation during the trial, limit supplemental vitamin D to ≤1000 IU/day and supplemental calcium to ≤1200 mg/d during the trial, and achieve 75% compliance during the 2-month placebo run-in phase (taking at least 75% of study pills). Additional exclusion criteria for our failure time analysis included a lifetime history of depression, depression treatment (anti-depressant use or receiving counseling) within the past 2 years, selective serotonin reuptake inhibitors (SSRI) use, and unclear history of depression at baseline.

Follow-up Procedures

At baseline, annually for 4 years post-randomization, and after the end of randomized treatment in January of 2021, participants were administered questionnaires via REDCap or mail to assess study adherence, adverse effects, updated medical history, and relevant lifestyle, clinical and dietary risk factors. Participants randomized during the later years of the parent trial did not complete the maximum of 5 post-baseline annual questionnaires (n = 15,365).

Primary Outcomes

The Mental Health Inventory 5 (MHI-5), an abbreviated version of the MHI-38 and one of the eight subscales of the 36-Item Short Form Survey (SF-36), was used to assess our first primary outcome of subjective mental health. The MHI-5 was included in questionnaires administered at randomization and at 1-year post randomization. Designed to assess mental health outcomes in adults, MHI-5 scores were chosen based on validation studies showing that MHI-5 scores are inversely associated with validated depression severity scales such as the Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale (HAM-D).[26,27] Other studies show that the MHI-5 is a valid tool for screening for mood disorders and a threshold cutoff of MHI-5 $\leq$52 has a high sensitivity and specificity to identify individuals with depression.[28,29] Additionally, lower MHI-5 scores have been shown to be associated with risk factors for depression and improvements in MHI-5 scores have been associated with anti-depressant treatment response in outpatients aged >65 years, providing further support for the validity of MHI-5 as a tool for assessing mental health outcomes in older adults.[27,30] MHI-5 scores are standardized to a 100-point scale, with lower scores indicating poorer subjective mental health. MHI-5 questions and scoring criteria are contained in Supplement 1.

Information relevant to our second primary outcome, risk of incident late-life depression, was collected at baseline (lifetime diagnosis of depression, current selective serotonin reuptake inhibitor [SSRI] use and depression treatment [anti-depressant use and/or receiving counseling] within past 2

years) and via annual follow-up questionnaires (depression diagnosis and/or depression treatment within past year). Depression diagnosis within the past year, but not depression treatment within the past year, was assessed at the end of randomized treatment via the final follow-up questionnaire.

Statistical Analyses

The primary aims of our analysis were to test our hypothesis that cocoa extract supplementation improves self-reported mental health outcomes and reduces the risk of incident late-life depression in older adults. Five analyses evaluated effect modification based on *a priori* factors (sex, baseline MHI-5 scores, depression treatment, lifetime diagnosis of depression, and depression treatment and/or lifetime diagnosis of depression) with respect to self-reported mental health outcomes. Three analyses examined effect modification by *a priori* factors (sex, baseline MHI-5 scores, and time since randomization) with respect to incident late-life depression.

To evaluate the effect of cocoa extract supplementation on self-reported mental health outcomes, we conducted a multivariate linear regression analysis using Mental Health Inventory 5 (MHI-5) scores at 1 year as the outcome variable and adjusting for design features – multivitamin arm and recruitment sources. Effect modification by sex and anti-depressant use on cocoa extract supplementation was assessed using linear regression models with multiplicative interaction terms between treatment and predictor variables of interest, adjusting for design features (multivitamin arm and recruitment source). As clear information on anti-depressant use was unavailable (data on recent treatment for depression did not distinguish between anti-depressant use or counseling), effect modification by anti-depressant use was triangulated via separate linear regression models using cocoa extract * depression treatment, cocoa extract * depression, or cocoa extract * depression and/or depression-treatment as interaction terms. In the event of a significant interaction term, effects within pre-specified subgroups were considered.

Sensitivity analyses fully adjusting for relevant covariates including baseline MHI-5 scores, lifetime diagnosis of depression, depression treatment (anti-depressant use and/or counseling within the

past 2 years and/or regular SSRI use), age, BMI, smoking status, physical activity, education level, alcohol intake, use of NSAIDs, cholesterol-lowering medication (statins and non-statin cholesterol-lowering drugs), history of congestive heart failure, vitamin D use, history of hypertension, and history of cancer were conducted to evaluate the robustness of our results. Further, *post-hoc* sensitivity analyses addressed 1) differences in missingness of 1-year MHI-5 outcome data between treatment groups using multiple imputation to impute missing outcome data and 2) robustness of our linear regression model to the violation of normality of residuals using quantile regression and logistic regression models.

The second part of our analysis evaluated the effects of cocoa extract supplementation on the risk of incident late-life depression. We conducted a failure time analysis using a Cox Proportional Hazards model, stratifying on design features – recruitment source and multivitamin arm. Depression diagnosis within the past year at follow-up was used as an outcome variable. Depression event dates were the questionnaire return date. Follow-up time was censored at time of last submitted follow-up form with depression diagnosis information, end of study, or death, whichever came first. Participants with a prior lifetime diagnosis of depression, unclear history of depression, receiving depression treatment (anti-depressant use and/or counseling) within 2 years prior to baseline, and/or were regularly taking SSRIs at baseline were excluded from this analysis. The proportional hazards assumption was tested using a goodness-of-fit graphical approach and Schoenfeld residuals. A potential interaction between cocoa extract and time since randomization was tested using a Cox-extended model. Effect modification by sex and baseline MHI-5 scores on cocoa extract was assessed using Cox PH models containing multiplicative interaction terms and adjusting for design features.

Sensitivity analyses fully adjusting for relevant covariates, including baseline MHI-5 scores, age, BMI, smoking status, physical activity, education level, alcohol intake, use of NSAIDs, cholesterol-lowering medication (statins and non-statin cholesterol-lowering drugs), history of congestive heart failure, vitamin D use, history of hypertension, and history of cancer, were conducted to evaluate the

robustness of our results. Furthermore, *post-hoc* sensitivity analyses were conducted including initiation of depression treatment as events.

Statistical significance was assessed using 2-sided P-values ≤0.05. P-values or confidence intervals were not adjusted for multiple comparisons. Thus, we would expect <1 interaction to be significant by chance.

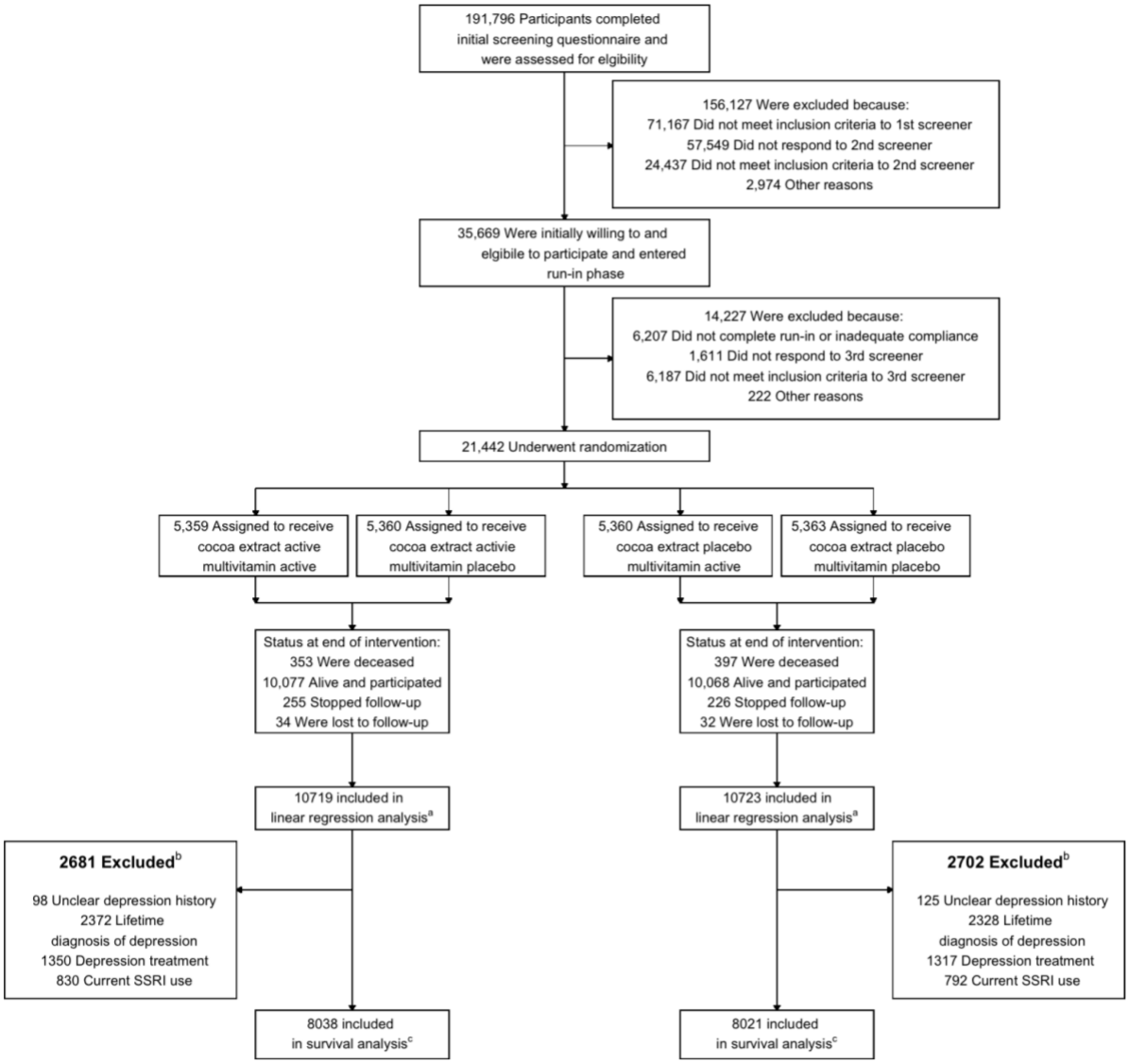
All data analyses were conducted in R version 10.0.14393.

Results

Among the 21442 participants, 10723 were randomized to placebo (5360 multivitamin active, 5363 multivitamin placebo) and 10719 (5360 multivitamin active, and 5359 placebo) were randomized to cocoa extract supplementation and were eligible for the linear regression analysis. The baseline characteristics of participants were similar between treatment groups (Table 1). The mean age of participants was 72.1 [SD: 6.6], women comprised 59% of sample participants and 90% of the participants self-identified as white. 22% of participants had a lifetime diagnosis of depression at baseline, 14% had received depression treatment (anti-depressants and/or counseling) within the past 2 years and/or were currently taking SSRIs, and 3.7% had a baseline MHI-5 score ≤52.

23% of participants had a prior lifetime diagnosis of depression, unclear history of depression, received depression treatment (anti-depressants and/or counseling) within the past 2 years, and/or were regularly taking SSRIs at baseline and were ineligible for the failure time analysis. Altogether, 5838 participants were excluded from the failure time analysis, leaving 16059 participants – 8021 initially randomized to placebo (4011 multivitamin active, 4010 multivitamin placebo), and 8038 (4059 multivitamin active, 3979 multivitamin placebo) randomized to cocoa extract. Baseline characteristics of eligible patients are described in Supplement 2. Figure 1 summarizes the screening protoco1s for both analyses.

Figure 1: Screening, randomization, and follow-up of participants



Footnote:

[a]Included in multivariate linear regression analysis investigating MHI-5 scores at 1-year
[b]Some participants met more than one exclusion criteria
[c]Included in failure time analysis investigating risk of incident late-life depression

Table 1. Baseline characteristics of participants enrolled in the COSMOS trial			
	Total (n = 21442)	Placebo (n = 10723)	Cocoa (n = 10719)
Randomized to active multivitamin (%)	50.0%	50.0%	50.0%
Baseline MHI-5 scores, mean ± SD	83.3% ± 13.2	83.4 ± 13.2	83.3 ± 13.2
Self-reported lifetime diagnosis of depression	22.1%	21.9%	22.3%
Depression treatment (antidepressants or counseling)[a]	14.3%	14.2%	14.5%
Female sex	59.1%	59.0%	59.1%
Age, mean ± SD, y	72.1 ± 6.6	72.1 ± 6.6	72.1 ± 6.6
BMI, mean ± SD, kg/m^2	27.7 ± 5.4	27.7 ± 5.5	27.6 ± 5.4
Race/Ethnicity[b]			
White	90.0%	90.2%	89.8%
African American	5.3%	5.3%	5.2%
Asian/Pacific Islander	2.3%	2.1%	2.6%
American Indian/Alaska Native	0.3%	0.3%	0.3%
Multiracial/other/unknown or not reported	2.1%	2.1%	2.2%
Education			
High school diploma/GED or less	10.8%	10.9%	10.7%
Attended or graduated college	40.9%	41.1%	40.8%
Post-college	48.3%	48.0%	48.5%
Smoking status			
Never	54.7%	54.9%	54.6%
Past	41.3%	41.0%	41.6%
Current	4.0%	4.1%	3.8%
Alcohol use			
Rarely/Never	29.7%	30.0%	29.4%
Daily	26.7%	26.8%	26.6%
Weekly	36.1%	35.7%	36.6%
Monthly	7.4%	7.4%	7.4%
Vitamin D supplementation			
None	37.6%	38.1%	37.2%
<1000 IU	41.0%	40.8%	41.1%
>1000 IU	20.9%	20.9%	20.8%
Physical Activity (MET hours/week)[c]	24.0	23.7	24.2
History of diabetes	13.4%	13.5%	13.2%
History of hypertension	58.1%	58.3%	57.9%
Cholesterol-lowering medication use	44.5%	44.4%	44.5%
NSAID use	29.0%	29.3%	28.7%
No. of cardiovascular risk factors[d]			
0-1	43.0%	43.2%	42.8%
2	29.4%	29.2%	29.6%
>/= 3	27.5%	27.5%	27.5%
History of CVD[e]	5.9%	6.0%	5.8%
History of heart failure	1.7%	1.8%	1.6%
History of cancer excluding non-melanoma skin cancer	16.6%	16.6%	16.6%

Footnote:

[a]Within the past 2 years, includes selective serotonin-reuptake inhibitor (SSRI) use, not necessarily for depression, at baseline

[b]Ethnic group and race were self-reported by participants. Multiracial participants self-identified with >1 race. Participants of other race or unknown race self-identified with those categories.

[c]Includes activity from exercise and stairs

[d]Cardiovascular risk factors were history of hypertension, diabetes, taking cholesterol-lowering medication, smoking (ever), and parental history of early myocardial infarction (<65 y).

[e]Defined as history at baseline of CABG/PCI, unstable angina, carotid artery surgery/stenting, or peripheral artery surgery/stenting

Cocoa Extract & Subjective Mental Health Outcomes

Mean MHI-5 scores were similar between the placebo group (83.4) and cocoa extract (83.3) group after 1 year. No effect of cocoa extract supplementation was found on MHI-5 scores at 1-year after adjusting for design features (β = -0.13, 95% CI: -0.49, 0.24) (Table 2). Outcome data were missing for <10% of participants and varied slightly by randomization (8.1% in placebo group vs 8.9% in cocoa group, p = 0.03).

Effect Modifiers of Cocoa Extract on Subjective Mental Health Outcomes

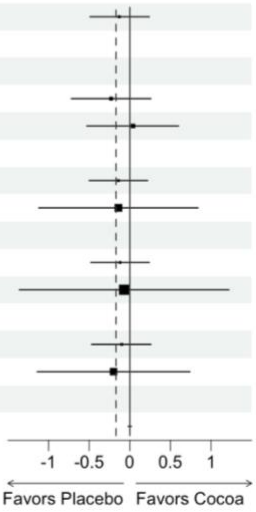
No effect modification was observed between cocoa extract and sex, baseline MHI-5 score, depression, depression treatment, or depression and/or depression treatment (p-interaction $\geq$ 0.48) (Table 2).

Sensitivity Analyses

A sensitivity analysis using multiple imputation to impute missing outcome data confirmed our findings (β = -0.12, p = 0.52). Sensitivity analyses fully adjusting for relevant covariates were consistent with our findings, aside from a significant interaction observed for cocoa extract and depression treatment (p-interaction = 0.03) (Supplement 4). Among those not receiving depression treatment, cocoa extract led to a significant decrease in 1-year MHI-5 scores (β = -0.34, 95% CI: -0.63, -0.0008), while no significant effect was observed in individuals receiving depression treatment (β = 0.67, 95% CI: -0.40, 1.73) (Supplement 4).

Table 2. Multivariable Linear Regression Model – Effect of cocoa extract supplementation on MHI-scores at 1 year, adjusted for design features

Subgroup	No. of participants Placebo (N=10719)	Cocoa (N=10723)	β (95% CI)	P	β (95% CI)
Overall Effect on 1-year MHI-5 outcomes, adjusted for design features[a]	9857	9766	-0.13 (-0.49, 0.24)	0.51	
Participant Characteristics					
Sex				0.48	
Female	5813	5744	-0.23 (-0.72, 0.26)		
Male	4044	4022	0.04 (-0.53, 0.60)		
Lifetime Diagnosis of Depression				0.99	
No	7640	7568	-0.14 (-0.50, 0.22)		
Yes	2112	2116	-0.14 (-1.12, 0.84)		
Depression Treatment				0.90	
No	8312	8247	-0.12 (-0.48, 0.24)		
Yes	1321	1338	-0.07 (-1.36, 1.22)		
Lifetime Diagnosis of Depression or Depression Treatment				0.83	
No	7422	7374	-0.10 (-0.47, 0.26)		
Yes	2242	2238	-0.20 (-1.14, 0.74)		
Baseline MHI-5[b]				0.93	
Per 1-point score increase	9614	9550	0.001 (-0.02, 0.02)		



Footnote:
[a]Summary statistics were from multivariate linear regression analyses adjusted for recruitment source and multivitamin randomization. P-values and CIs were not adjusted for multiple comparisons.
[b]Baseline MHI-5 scores treated as continuous variable.
[c]The assumption of normality of residuals was not satisfied by the model. Quantile regression and logistic regression models (not shown) provide evidence for robustness of this model to this violation.

Cocoa Extract & Incident Depression

Incident depression events were reported in 291 individuals in the placebo group (10.4/1000 person-years) and 267 individuals in the cocoa group (9.6/1000 person-years) (Table 3). No significant effect of cocoa extract supplementation on incident depression was found after adjusting for design features (HR = 0.92, 95% CI: 0.78, 1.09) (Table 3). Cumulative incidence curves showed lack of separation between treatment groups over the entire follow-up (Figure 2). Missingness of outcome data was not related to randomization.

Effect Modifiers of Cocoa Extract on Incident Late-life Depression

A Cox-extended model showed no evidence for an effect of time since randomization on the relationship between cocoa extract and incident late-life depression ($p = 0.67$). No interaction between cocoa extract and baseline MHI-5 or sex was found (p-interaction ≥ 0.18) (Table 3). Sex-specific

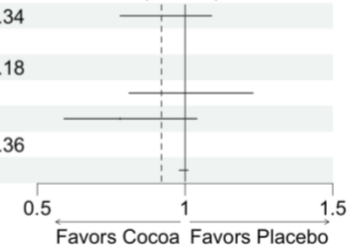
cumulative incidence curves showed no separation between treatment groups among women but did show slight divergence between treatment groups in men (Figure 3), although subgroup analyses showed no significant reduction in incident late-life depression in men (HR = 0.78, 95% CI: 0.59, 1.04) (Table 3). Baseline characteristics for men and women subgroups are described in Supplement 3.

Sensitivity Analyses

All effects of cocoa extract on incident late-life depression were consistent with sensitivity analyses fully adjusting for covariates (Supplement 5) and including depression treatment initiation as events (providing an additional 4 events) (Supplement 6).

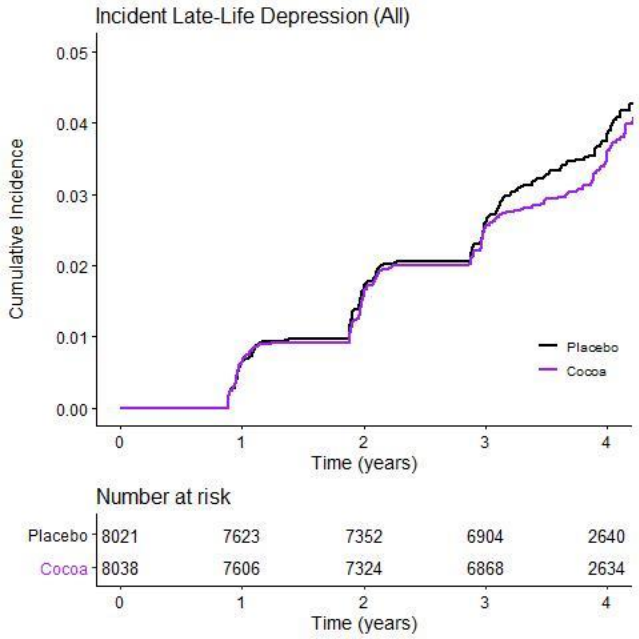
Table 3. Cox Proportional Hazard Model – Effect of cocoa extract on risk of incident late-life depression, adjusted for design features

	No. of participants with event				
Subgroup	**Placebo (N=8021)**	**Cocoa (N= 8038)**	**HR (95% CI)**	**P**	**HR (95% CI)**
Overall Effect on Incident Late-life Depression[a]	291	267	0.92 (0.78, 1.09)	0.34	
Participant Characteristics					
Sex				0.18	
Female	182	181	1.00 (0.81, 1.23)		
Male	109	86	0.78 (0.59, 1.04)		
Baseline MHI-5[b]				0.36	
Per 1-point score increase	279	262	0.99 (0.98, 1.01)		



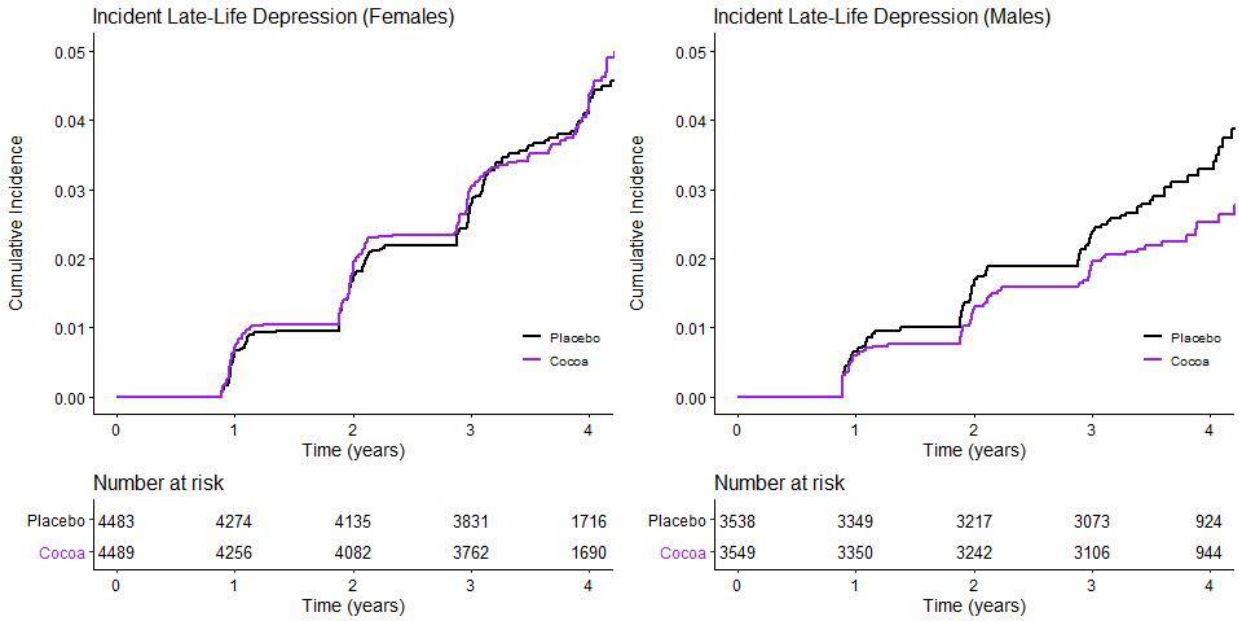
Footnote:
[a]Summary statistics were from Cox Proportional Hazards models that stratified baseline hazard functions by multivitamin randomization and recruitment cohort. P-values and CIs were not adjusted for multiple comparisons.
[b]Baseline MHI-5 scores treated as continuous variable.

Figure 2. Cumulative Incidence Curves for incident late-life depression – Cocoa Extract vs Placebo[a]



Footnote:
[a]Among the 16,059 eligible participants without a history of depression, receiving depression treatment (anti-depressant treatment and/or counseling) within past 2 years, current SSRI use, or unclear history of depression. Goodness-of-fit graphical approach and Schoenfeld residuals support satisfaction of proportional hazards assumption.

Figure 3. Sex-specific Cumulative Incidence Curves for incident late-life depression – Cocoa Extract and Placebo[a]



Footnote:
[a]Sex-specific cumulative incidence curves from the 16,059 eligible participants without a history of depression, receiving depression treatment (anti-depressant treatment and/or counseling) within past 2 years, current SSRI use, or unclear history of depression. Goodness-of-fit graphical approach and Schoenfeld residuals support satisfaction of proportional hazards assumption.

Discussion

In a secondary analysis of 21,442 older adults enrolled in the COSMOS trial, cocoa extract did not result in a significant difference in MHI-5 scores after 1 year. Contrary to previous studies showing that cocoa extract improves positive affect – calmness and contentedness – in middle-aged, healthy adults, the findings do not support a role for cocoa extract supplementation in improving subjective mental health outcomes in older adults[11].

In a failure time analysis of 16,059 participants without a lifetime diagnosis of depression, not receiving depression treatment, and who were not taking SSRIs, cocoa extract did not result in a significant difference in incident depression events over a median follow-up of 3.6 years. These findings do not support the use of cocoa extract supplementation as a prophylactic treatment for late-life depression. Although this is the first clinical trial to evaluate the effects of cocoa extract supplementation as a prophylactic treatment for late-life depression, our findings are in alignment with a prospective study finding no association between flavanol consumption and risk of incident late-life depression in middle-aged and older women.[25]

In ancillary studies, including the COSMOS-Web and COSMOS-Mind trials, the effects of cocoa flavanols on cognitive function in older adults were evaluated. These results are of primary interest because cognitive impairment, particularly in the domains of executive function and processing speed, has been described in a subset of patients with LLD and may be a core contributor to the development of LLD.[2,31] Furthermore, poor executive function predicts poor antidepressant response and early relapse and recurrence in LLD.[2]

In the COSMOS-Web trial, an ancillary trial of the COSMOS trial investigating the effects of cocoa extract supplementation on cognitive function, cocoa flavanols improved performance on a hippocampal-dependent memory, but not prefrontal-dependent cognition, after 1 year in individuals with poor dietary quality (ranking in the lowest tertile of the Healthy Eating Index) or low habitual flavanol

consumption, confirming the results of a preliminary 12-week clinical trial conducted by the research group.[32, 33] These results point to a potential beneficial effect on cognition in individuals with LLD presenting with hippocampal-dependent cognitive impairments and poor dietary quality or low flavanol consumption, although these regional-specific deficits have yet to be evaluated for their relevance to the pathophysiology of LLD.

On the other hand, the COSMOS-Mind trial found no effect of cocoa flavanols on episodic memory, global cognition, or executive function.[34] These findings contrast with the Cocoa, Cognition, and Aging (CoCoA) Study which showed acute improvements in executive function, processing speed, and verbal fluency with higher doses of cocoa flavanol supplementation.[35] Thus, it is possible that doses of cocoa flavanols insufficient to improve cognitive function in this trial are insufficient to confer reductions in incident depression risk.

Strengths of the COSMOS trial include its randomized nature, large sample size, long duration, high follow-up rate, and the use of a 2-month placebo run-in to increase adherence to study protocols. Further strengths of this study include >99% complete data on participants' lifetime history of depression and >90% data on 1-year MHI-5 outcomes.

The limitations of this analysis must be taken into consideration. First, it should be noted that the primary purpose of the COSMOS trial was to investigate cardiovascular and cancer outcomes. Thus, this trial did not randomize nor collect data on baseline characteristics that could affect our primary outcomes – i.e., mood, neurocognitive, and psychiatric diagnoses, psychiatric medications, clinical hypothyroidism, and family history of mood, neurocognitive and/or psychiatric disorders. Nevertheless, randomization should assure reasonable balance on unmeasured factors. Second, data was not collected on baseline status of depression, prohibiting failure time analyses assessing recurrent and total late-life depression. Given that among men, 375 and 298 total depression events were reported in the placebo and cocoa groups, respectively (Supplement 7), there may have been a significant treatment by sex interaction for

total and/or recurrent depression if events carrying over from baseline could have been excluded. Third, given that survey questions only assessed whether participants had received depression treatment (including counseling), rather than anti-depressants specifically, we were unable to adequately assess the interaction effects between cocoa extract and anti-depressant use.

The generalizability of these results to other populations should also be taken into consideration. Compared to prevalences observed in previous observational studies, participants enrolled in the COSMOS trial had an abnormally high prevalence of lifetime diagnosis of depression (22.1%), double the prevalence of major depressive disorder (10.6%) in adults >60 years old found in the National Comorbidity Survey Replication (NCS-R).[36] Additionally, it should also be noted that the parent COSMOS trial excluded individuals with a previous MI, stroke, or recently diagnosed cancer within the past 2 years. Given that cerebrovascular dysfunction is implicated in the pathophysiology of late-life depression and MI and stroke patients are at a higher risk of depression later in life, individuals in this cohort would be expected to be at a lower risk of late-life-depression. Interestingly, incident depression rates in this cohort (10.4/1000 person-years in the placebo group) were comparable to other large-scale clinical trials in older adults such as the VITAL-DEP trial (10.8/1000 person-years), although the latter trial included clinically relevant depressive symptoms (defined as PHQ-8 score ≥10) as events, did not exclude participants with a history of stroke, and had a lower mean age (67.5 years).[37]

Additional studies looking at the effects of cocoa flavanols on the various subtypes of depression are needed. Studies investigating the effects of cocoa extract on non-affective dimensions of depression may also be of interest given the predominance of somatic symptoms in late-life depression compared to depression affecting younger adults.[1] In our study, among individuals who reported a diagnosis within the past year at 1-year follow-up, only ~25% had an MHI-5 score ≤52, suggesting that MHI-5 scores may not be representative of overall mental health in this population. Interaction effects between cocoa flavanols and anti-depressant use must also be further evaluated, preferably with a particular focus on specific anti-depressant classes that have shown efficacy in preventing and treating late-life depression. Lastly, given

that the COSMOS trial did not collect data on baseline diagnoses of depression, additional studies are necessary to investigate the effects of cocoa extract recurrent on early-onset late-life depression.

Conclusions

Among adults >60 years old free of MI, stroke, and recently diagnosed cancer, cocoa extract was not effective in improving MHI-5 scores or reducing the risk of incident depression. These findings do not support the use of cocoa extract in improving subjective mental health outcomes or as a prophylactic treatment for late-life depression.

Supplementary Data

Table S1. Mental Health Inventory 5 (MHI-5) questions and scoring criteria

How much of the time during the past 4 weeks...	All of the time = 1	Most of the time = 2	A good bit of the time = 3	Some of the time = 4	A little of the time = 5	None of the time = 6
Have you been a nervous person?						
Have you felt so down in the dumps that nothing could cheer you up?						
Have you felt downhearted and blue?						
How much of the time during the past 4 weeks...	All of the time = 6	Most of the time = 5	A good bit of the time = 4	Some of the time = 3	A little of the time = 2	None of the time = 1
Have you felt calm and peaceful?						
Have you been a happy person?						

Footnote: Scores are totaled and standardized to a 100-point scale.

Table S2. Baseline characteristics of patients without a lifetime diagnosis of depression, depression treatment and/or regularly taking SSRIs			
	Total (n = 16059)	Placebo (n = 8021)	Cocoa (n = 8038)
Randomized to active multivitamin (%)	50.3%	50.0%	50.5%
Baseline MHI-5 scores, mean ± SD	85.5 ± 11.3	85.5 ± 11.3	85.4 ± 11.3
Female sex	55.9%	55.9%	55.9%
Age, mean ± SD, y	72.2 ± 6.7	72.1 ± 6.7	72.2 ± 6.8
BMI, mean ± SD, kg/m^2	27.5 ± 5.2	27.6 ± 5.3	27.4 ± 5.2
Race/Ethnicity[a]			
White	89.5%	89.6%	89.5%
African American	5.6%	5.7%	5.4%
Asian/Pacific Islander	2.7%	2.4%	3.0%
American Indian/Alaska Native	0.2%	0.2%	0.2%
Multiracial/other/unknown or not reported	2.0%	2.1%	1.9%
Education			
High school diploma/GED or less	10.7%	10.7%	10.7%
Attended or graduated college	41.3%	41.7%	40.8%
Post-college	48.0%	47.8%	48.6%
Smoking status			
Never	56.7%	56.9%	56.5%
Past	39.8%	39.4%	40.2%
Current	3.5%	3.7%	3.3%
Alcohol use			
Rarely/Never	28.6%	29.1%	28.2%
Daily	27.4%	27.8%	27.0%
Weekly	36.8%	35.8%	37.9%
Monthly	7.2%	7.4%	6.9%
Vitamin D supplementation			
None	38.6%	38.8%	38.4%
<1000 IU	40.7%	40.4%	41.0%
>1000 IU	20.7%	20.8%	20.6%
Physical Activity (MET hours/week)[b]	24.9	24.3	25.4
History of diabetes	12.7%	12.9%	12.3%
History of hypertension	57.2%	57.8%	56.6%
Cholesterol-lowering medication use	43.3%	43.4%	43.2%
NSAID use	27.1%	27.5%	26.7%
No. of cardiovascular risk factors[c]			
0-1	44.7%	44.6%	44.7%
2	29.1%	29.1%	29.1%
>/= 3	26.2%	26.2%	26.2%
History of CVD[d]	5.7%	5.7%	5.6%
History of heart failure	1.5%	1.6%	1.4%
History of cancer excluding non-melanoma skin cancer	16.7%	16.5%	16.9%

Footnote:

[a]Ethnic group and race were self-reported by participants. Multiracial participants self-identified with >1 race. Participants of other race or unknown race self-identified with those categories.

[b]Includes activity from exercise and stairs

[c]Cardiovascular risk factors were history of hypertension, diabetes, taking cholesterol-lowering medication, smoking (ever), and parental history of early myocardial infarction (<65 y).

[d]Defined as history at baseline of CABG/PCI, unstable angina, carotid artery surgery/stenting, or peripheral artery surgery/stenting

Table S3. Baseline characteristics of patients without a lifetime diagnosis of depression, depression treatment and/or regularly taking SSRIs by sex			
	Total (n = 16059)	Female (n = 8972)	Male (n = 7087)
Randomized to active multivitamin (%)	50.3%	50.4%	50.1%
Baseline MHI-5 scores, mean ± SD	85.5 ± 11.3	85.3 ± 11.5	85.7 ± 11.2
Age, mean ± SD, y	72.2 ± 6.7	74.6 ± 6.1	69.1 ± 6.2
BMI, mean ± SD, kg/m^2	27.5 ± 5.2	27.2 ± 5.6	27.8 ± 4.7
Race/Ethnicity[a]			
White	89.5%	89.0%	90.2%
African American	5.6%	6.3%	4.7%
Asian/Pacific Islander	2.7%	2.3%	3.2%
American Indian/Alaska Native	0.2%	0.2%	0.2%
Multiracial/other/unknown or not reported	2.0%	2.2%	1.8%
Education			
High school diploma/GED or less	10.0%	14.6%	5.9%
Attended or graduated college	41.3%	42.7%	39.5%
Post-college	48.0%	42.7%	54.7%
Smoking status			
Never	56.7%	58.4%	54.5%
Past	39.8%	38.8%	41.1%
Current	3.5%	2.8%	4.4%
Alcohol use			
Rarely/Never	28.6%	33.5%	22.1%
Daily	27.4%	20.6%	36.5%
Weekly	36.8%	37.6%	35.8%
Monthly	7.2%	8.3%	5.6%
Vitamin D supplementation			
None	38.6%	27.5%	52.5%
<1000 IU	40.7%	45.7%	34.4%
>1000 IU	20.7%	26.8%	13.1%
Physical Activity (MET hours/week)[b]	24.9	23.0	27.2
History of diabetes	12.7%	11.6%	14.1%
History of hypertension	57.2%	57.1%	57.4%
Cholesterol-lowering medication use	43.3%	39.1%	48.7%
NSAID use	27.1%	29.7%	23.8%
No. of cardiovascular risk factors[c]			
0-1	44.7%	47.0%	41.7%
2	29.1%	29.3%	28.9%
>/= 3	26.2%	23.7%	29.4%
History of CVD[d]	5.7%	4.1%	7.7%
History of heart failure	1.5%	1.5%	1.5%
History of cancer excluding non-melanoma skin cancer	16.7%	17.6%	15.6%

Footnote:

[a]Ethnic group and race were self-reported by participants. Multiracial participants self-identified with >1 race. Participants of other race or unknown race self-identified with those categories.

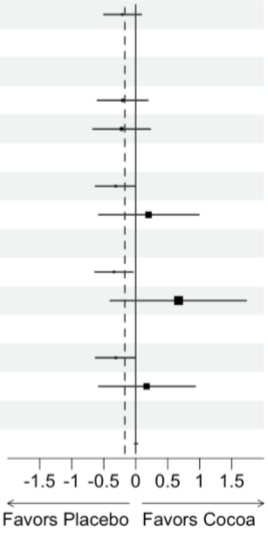
[b]Includes activity from exercise and stairs

[c]Cardiovascular risk factors were history of hypertension, diabetes, taking cholesterol-lowering medication, smoking (ever), and parental history of early myocardial infarction (<65 y).

[d]Defined as history at baseline of CABG/PCI, unstable angina, carotid artery surgery/stenting, or peripheral artery surgery/stenting

Table S4. Multivariable Linear Regression Model – Effect of cocoa extract supplementation on MHI-scores at 1 year, fully adjusted for covariates

Subgroup	No. of participants Placebo (N=10719)	Cocoa (N=10723)	β (95% CI)	P	β (95% CI)
Overall Effect on 1-year MHI-5 outcomes, fully adjusted[a]	8071	8026	-0.21 (-0.50, 0.09)	0.17	
Participant Characteristics					
Sex				0.96	
Female	4746	4750	-0.20 (-0.60, 0.19)		
Male	3325	3276	-0.22 (-0.67, 0.23)		
Lifetime Diagnosis of Depression				0.20	
No	6346	6310	-0.31 (-0.63, -0.0008)		
Yes	1725	1716	0.20 (-0.58, 0.99)		
Depression Treatment				0.03	
No	6987	6942	-0.34 (-0.64, -0.04)		
Yes	1084	1084	0.67 (-0.40, 1.73)		
Lifetime Diagnosis of Depression or Depression Treatment				0.20	
No	6242	6217	-0.31 (-0.63, 0.0003)		
Yes	1829	1809	0.17 (-0.58, 0.93)		
Baseline MHI-5[b]				0.72	
Per 1-point score increase	8071	8026	0.004 (-0.02, 0.03)		

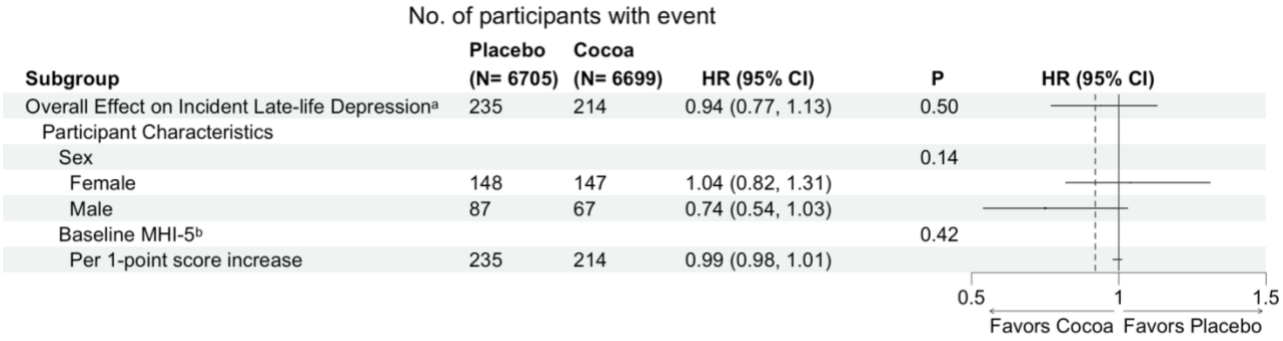


Footnote:

[a]Summary statistics were from multivariate linear regression analyses adjusted for multivitamin randomization, recruitment source, sex, age, smoking status, baseline MHI-5 scores, BMI, physical activity level, vitamin D intake, alcohol intake, and educational level, NSAID use, depression, depression treatment (anti-depressant use and/or counseling within past 2 years and/or SSRI use at baseline); history of cancer, hypertension, cholesterol lowering medication, and congestive heart failure. Individuals with any missing outcome or covariate data were excluded from analyses. P-values and CIs were not adjusted for multiple comparisons.

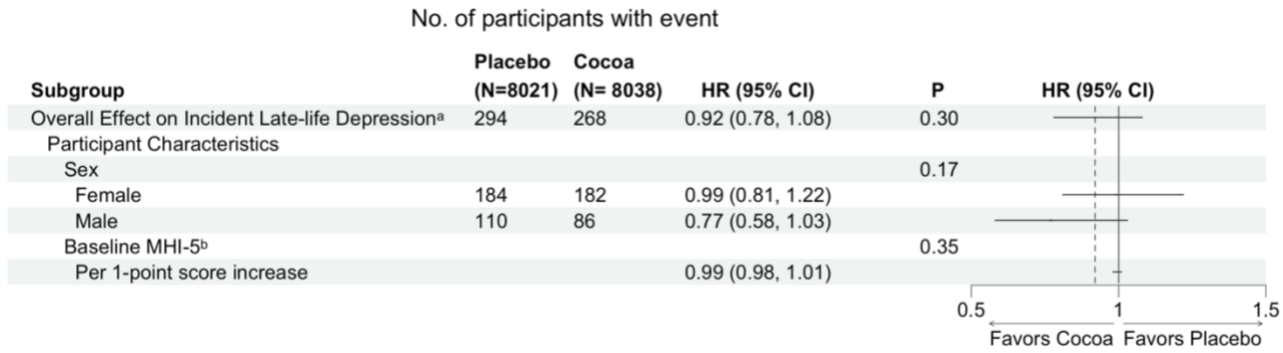
[b]Baseline MHI-5 scores treated as continuous variable.

Table S5. Cox Proportional Hazard Model – Effect of cocoa extract supplementation on risk of incident depression, fully adjusted for covariates



Footnote:
[a]Summary statistics were from Cox Proportional Hazards models that stratified baseline hazard functions by multivitamin randomization, recruitment source, sex, age, and smoking status, and further adjusted for baseline MHI-5 scores, BMI, physical activity level, vitamin D intake, alcohol intake, and educational level, NSAID use; history of cancer, hypertension, cholesterol lowering medication, and congestive heart failure. Individuals with any missing outcome or covariate data were excluded from analyses. P-values and CIs were not adjusted for multiple comparisons.
[b]Baseline MHI-5 scores treated as continuous variable.

Table S6. Cox Proportional Hazard Model – Effect of cocoa extract supplementation on risk of incident depression and/or depression treatment, adjusted for design features



Footnote:
[a]Summary statistics were from Cox Proportional Hazards models stratified by recruitment source and multivitamin randomization. P-values and CIs were not adjusted for multiple comparisons.
[b]Baseline MHI-5 scores treated as continuous variable.

Table S7. Number of individuals reporting a diagnosis of depression during follow		
	Individuals reporting a diagnosis of depression during follow-up[a]	**Individuals reporting a diagnosis of depression and/or initiation of depression treatment during follow-up[a,b]**
Total (n = 21,442)		
Placebo	1144	1154
Cocoa	1117	1123
Women (n = 8972)		
Placebo	769	778
Cocoa	819	824
Men (n = 7087)		
Placebo	375	376
Cocoa	298	299

Footnote:

[a]Baseline depression status was not assessed by survey questionnaires. Includes incident events, recurrent events, and events that may have been present upon randomization.

[b]Depression treatment includes inti-depressant use and/or counseling within past 2 years.

Table S8. Composition of the cocoa extract supplement tested in the COcoa Supplement and Multivitamin Outcomes Study (COSMOS)[1]	Cocoa extract supplement (2 capsules/day)
Total cocoa flavanols (DP 1-7) mg	500 ± 50
Total flavanol monomers	110 ± 10
(-)-epicatechin, mg	80 ± 10
(+)-catechin, mg	3 ± 2
(-)-catechin, mg	25 ± 5
Calories, kcal	<5
Total fat, g	<0.2
Saturated fat, g	<0.15
Total carbohydrates, g	<0.5
Sugars, g	0
Protein, g	<0.1
Fiber, g	<0.5
Theobromine, mg	50 ± 5
Caffeine, mg	15 ± 5

Footnote:

Composition details obtained from Supplementary Table 2 from parent COSMOS manuscript.[23] Plus-minus are means ± standard deviations.

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