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Baker LD, Manson JE, Rapp SR, et al. Effects of cocoa extract and a multivitamin on cognitive function: A randomized clinical trial. *Alzheimer's and Dementia*. 2022;10.1002/alz.12767.

What We Know, Think We Know, or Are Starting to Know

To date, the (poly)phenols in cacao have been some of the most promising flavonoids for potential meaningful impacts on human health ^(1,2).

In a very [recent Research Lecture](#), we discussed the evidence for cocoa flavanols in cognitive function. From an analysis of that evidence, we arrived at several specific conclusions:

- That inconsistencies in the evidence may reflect, among other factors, the small sample sizes of the studies.
- That doses of a minimum of 500mg total cocoa flavanols in combination with ~50mg epicatechins (the most common flavanol in cocoa).
- That there was no apparent benefit to doses of >750mg.
- That positive effects were typically observed for specific domains of cognitive function, specifically visuo-spatial tasks, processing speed, and memory, rather than for global cognition.
- That the balance of evidence was suggestive of effects of cocoa flavanols on specific domains of cognitive function, but inconclusive.

Generally, when the available evidence consists of small, short-term trials, the Research Gods demand a sacrifice: a large randomised controlled trial [RCT] over a period of years. In a previous [April 2022 Deepdive](#), we reviewed the recent Cocoa Supplement and Multivitamin Outcomes Study [COSMOS], the largest [~21,444 participants] and longest [~4yrs] intervention trial to date testing the effects of cocoa flavanols and/or multivitamin supplementation.

That paper reported the cardiovascular disease [CVD] results of the COSMOS trial, which found a 27% lower risk of CVD mortality, and 16% lower risk of major CVD events [defined as myocardial infarction (heart attack), stroke, and CVD mortality], compared to the placebo group. The COSMOS trial, however, also investigated cognitive outcomes. Let's take a Deepdive into the study...

The Study

The COSMOS-Mind trial investigated the effects of a cocoa extract supplement and/or a multivitamin supplement in men and women over 60yrs of age. 2,262 participants from the parent RCT were included in the following groups:

- **Active** cocoa + **active** multivitamin
- **Active** cocoa + **placebo** multivitamin
- **Placebo** cocoa + **active** multivitamin
- **Placebo** cocoa + **placebo** multivitamin

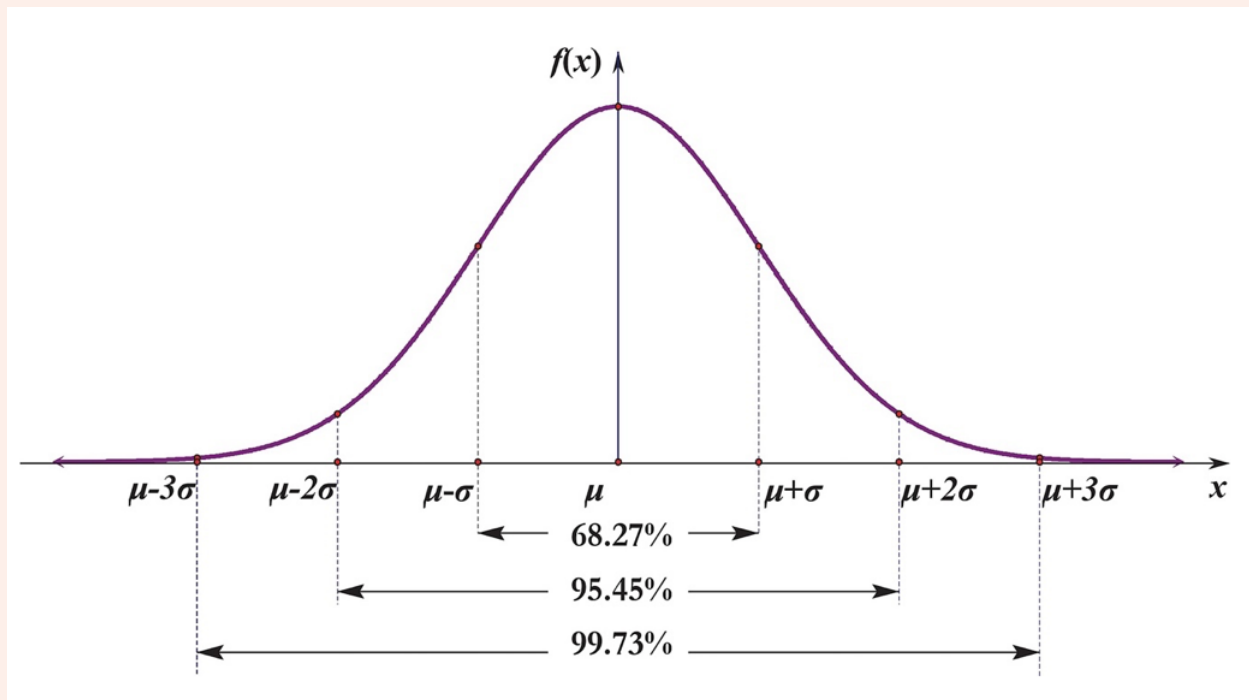
This type of design is known as a “2x2 factorial design”, meaning that each treatment has two levels [in this case, both the cocoa and multivitamin are active treatments *and* placebos]. Therefore, in the analysis active cocoa was compared to placebo cocoa, and active multivitamin was compared to placebo multivitamin.

The dose of cocoa flavanols was 500mg and 80mg epicatechin per day, while the multivitamin was the U.S. commercial brand, Centrum Silver®.

Cognitive tests were calculated as “z-score”*, or standard score [*to understand standard scores in more detail, read the ***Geek Box**, below]. The outcomes were reported as mean z-score change from baseline with 95% confidence intervals [95% CI; referred to as ‘range’ in **Results**, below].

*Geek Box: Using Z-scores in Research

To understand and interpret the findings in this study, it will be helpful to get to grips with standard scores, known in research as “z-scores”. Calculating z-scores is based on the normal distribution of data, as shown in the figure below.



A normal distribution appears as a bell-curve shape; ignore the Latin text, and just look at the lines and numbers. Dead centre we have the mean; this could be average height, weight, or blood pressure, in the population. Then the dashed lines either side of the mean are the standard deviation [SD] from the mean, i.e., what proportion of the data varies from the mean, and by how much. In a normal distribution, the variance is equal either side – above and below – the mean. Thus, you can see that 68.27% is within 1-SD from the mean; 95.45% within 2-SD; and 99.73% within 3-SD.

A z-score takes a set of data and standardises it to a normal distribution. Let's bring this to life with an example relevant to the present study. Assume we are interested in a cognitive test that assesses memory by testing the ability of participants to recall up to 10 words. Thus, the possible scores range from 0 to 10. Let's say the mean score in the study was 5, and the SD was 3.

One participant has scored 6; we might intuitively think that 6/10 is a good score, but how do we know how it compares to the overall study group? This is where researchers will calculate a z-score. The participant's z-score is calculated as; 6 [the score] minus 5 [the mean], divided by 3 [the SD]: 0.33. By calculating a z-score for every participant, it is then possible to use these scores to compare how well that participant did compared to others.

If another cognitive test was used that scored on a different scale, it would also be possible to calculate z-scores for that test to then compare how participants scored on both tests.

Results: 92% of participants enrolled in COSMOS-Mind completed the cognitive assessment at Year 1, (84% at Year 2, and 79% at Year 3. Overall, 77% completed the cognitive assessment in all 3 years of follow-up.

- **Effect on Global Cognition:** In the cocoa group, there was no significant difference in global cognitive scores compared between active and placebo groups [mean z-score difference of 0.03; range of -0.02 to 0.08]. However, the multivitamin group showed a significant difference in the active group compared to the placebo group [mean z-score difference 0.07; range of 0.02 to 0.12].

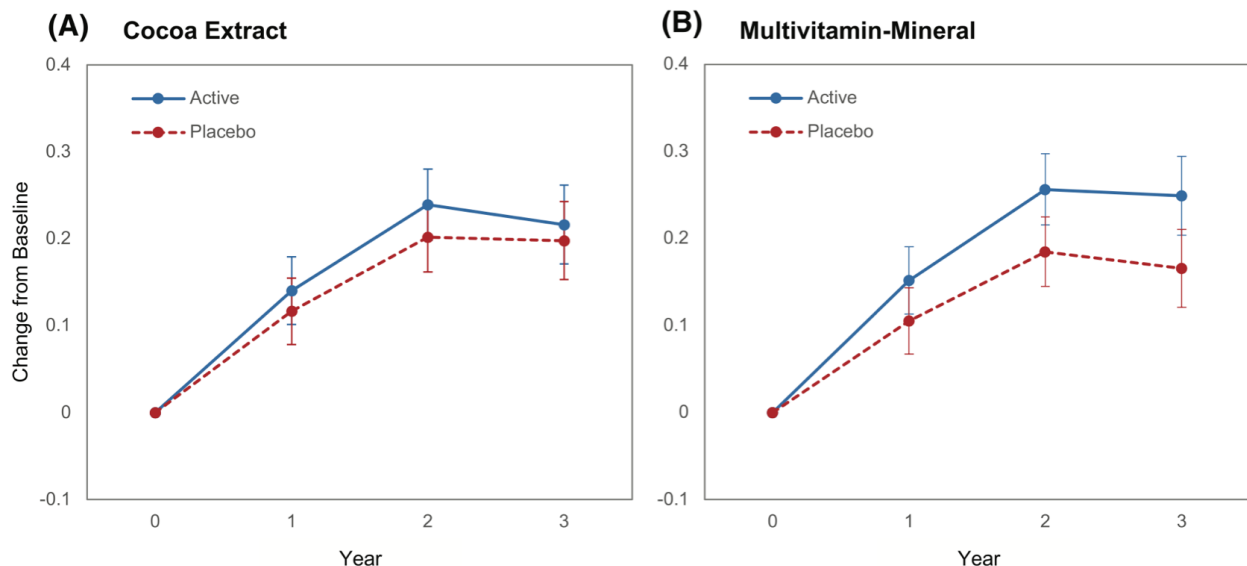


Figure from the paper showing [left] the difference in global cognition z-scores from baseline to Year 3 in the cocoa supplement group [blue line] compared to cocoa placebo group [red line], and [right] the difference in the multivitamin group [blue line] compared to multivitamin placebo [red line]. The data is shown as change from baseline. The multivitamin group showed a significant difference compared to the placebo group.

- **Effect on Specific Cognitive Domains – Episodic Memory:** The cocoa group showed no significant effect on episodic memory [mean z-score difference of 0.03; range of -0.04 to 0.09], however, the multivitamin group showed a significant difference [mean z-score difference of 0.06; range of 0.002 to 0.13] [see **figure**, below].
- **Effect on Specific Cognitive Domains – Executive Function:** The cocoa group showed no significant effect on episodic memory [mean z-score difference of 0.03; range of -0.02 to 0.08], however, the multivitamin group showed a significant difference [mean z-score difference of 0.06; range of 0.01 to 0.11] [see **figure**, below].

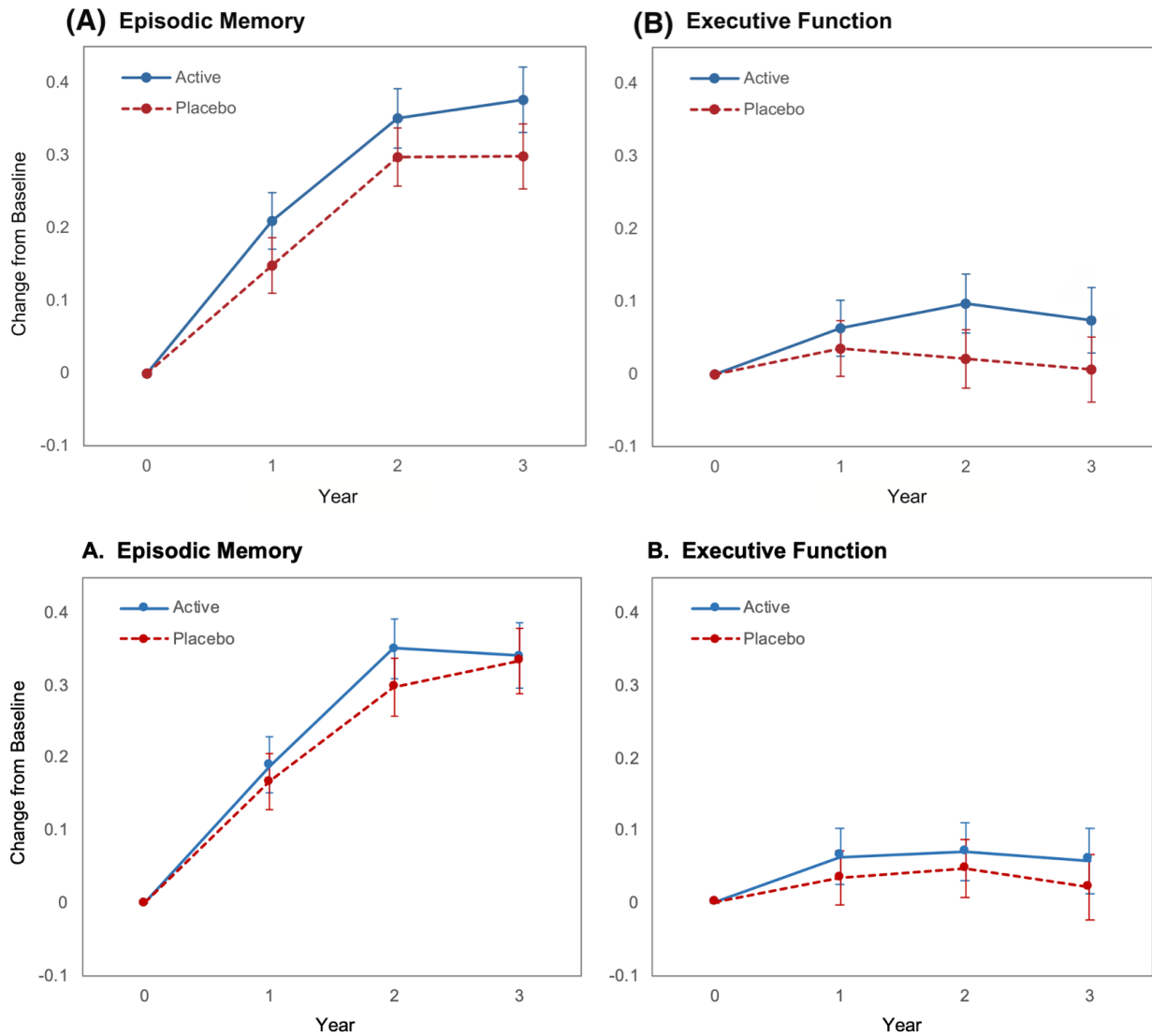


Figure from the paper showing **[top]** the difference episodic memory **[top left]** and executive function **[top right]** z-scores from baseline to Year 3 in the multivitamin group **[blue line]** compared to multivitamin placebo **[red line]**, and showing **[bottom]** the differences in the cocoa supplement group **[blue line]** compared to cocoa placebo group **[red line]**. In the executive function test for the multivitamin group, while there was an increase in z-scores in the supplement group it is likely that the decline in the placebo group influenced the outcome.

The Critical Breakdown

Pros: Randomisation was computer-generated and stratified by sex; investigators and participants were blinded to the allocation; assigned capsules [both cocoa and placebo] were mailed blinded to participants were calendar-labelled packages to enhance compliance. To be included in the study, participants had to complete a 2-month baseline run-in with placebo pills during which they were required to miss less than 8-days of taking the capsules [i.e., equivalent to ~75% compliance]. The study duration was ~4yrs, almost as good as it gets for a long-term nutrition intervention trial. Intention-to-treat analysis was used, which minimises the effects of missing participant data from introducing bias between groups. The subgroup analyses were pre-specified before the trial, which guards against “fishing” the data for findings. The exposure was also clearly defined; the use of a standardised cocoa extract meant that exact levels of (poly)phenols were provided and did not vary in composition of other bioactive compounds, e.g., theobromine, which may occur with food-based interventions. 77% completed the cognitive assessment in all 3 years of follow-up.

Cons: The primary analysis was not adjusted for any relevant potential covariates, e.g., sex, weight, or dietary intake. Indeed, no dietary analysis was conducted at all, so it is not possible to investigate how background diet may [or may not] have potentially influenced the outcomes. No baseline assessment of nutritional status was conducted; for such a large, well-designed trial this is frustrating because we have no ability to even make inferences about what nutrients in the multivitamin may have contributed to the observed effects. There were no statistical adjustments for multiple comparisons, which is where the accepted level of statistical significance is adjusted based on the number of different outcomes, to lower risk of “false positives”. Participants with missing data were more likely to be from underrepresented ethnic groups, lower education level, and more unhealthy behaviours, which may have introduced some bias in the data given the overall study group was White ethnicity and well-educated. In terms of external validity, the study sample was ~89% White ethnicity, 88% were third level educated, and 51% never smoked; thus, there are some generalisability issues regarding wider context and application to the U.S. general population.

Key Characteristic

The 3yr follow-up period of the present study is the most important characteristic of the study, however, it also must be considered in the context of conducting single, annual cognitive assessments. To be fair to the authors, they do draw attention to the potential issue could arise; if the effects of cocoa are more acute, then conducting a single annual cognitive assessment may have missed any acute effects of cocoa.

One may wonder why this approach was taken. The COSMOS-Mind trial was a pragmatic trial, delivering the tests by telephone in participants who had been screened for hearing acuity. This was all designed to increase the ease of participating in the study. But this begs the question; why not conduct the tests every 3-months across the year? Or 6-months, even? This could then allow for both a yearly average to be calculated, while also potentially being more sensitive to capture fluctuations over the year.

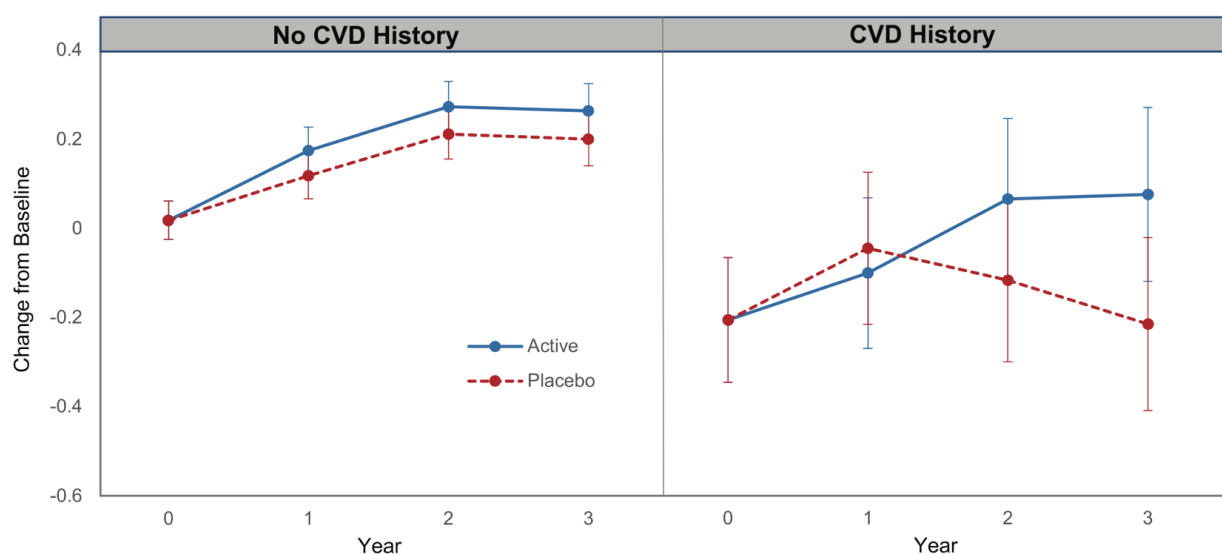
This is something to consider, because “cognition” is a broad term and includes both acute and chronic effects, and in terms of tests, reflects global cognition and specific domains. The evidence from human intervention trials to date has primarily been in acute studies – either 1 day or up to 8-weeks ^(3,4). Given the upper end of these previous studies, and the method of conducting the tests in this study, more regular testing would have provided some insights into more acute, short-term effects in addition to the annual outcomes.

Interesting Finding

The significant effect of the multivitamin supplement in participants with a history of CVD deserves some thought, given the truism that “what is good for the head is good for the heart”.

There are some interesting overlaps between the brain and cardiovascular research areas. For example, patients on statins to lower CVD risk have a significant 16% lower risk of total dementia and 29% lower risk of Alzheimer’s Disease ⁽⁵⁾. This may be mediated by lowering cholesterol, as high levels of cholesterol influence the development of plaque in the brain ⁽⁶⁾.

That is just an example, there is no way we can say from the present study whether there was any relationship between multivitamin use and CVD risk factors, i.e., we don’t know what the participant’s cholesterol levels were. And the fact that no medication use was adjusted for in the present study, with ~44% of the study group on statins, means we don’t know what potential interaction effects medication had.



What we *can* see from the above **figure** is that participants with a history of CVD had lower cognitive z-scores at baseline. However, the placebo group [red dashed line] decreased in their z-scores after Year 1, while the multivitamin group [blue solid line] increased across the duration of the study from baseline.

What may explain these effects? The authors state that it could be due to “*the potential treatment-related improvement in micronutrient levels in CVD-compromised individuals*”, which brings us back to one of the major limitations of the study; not actually assessing micronutrient levels at baseline. If individuals with CVD *did* have lower than adequate levels of micronutrients, we could expect that bolstering nutrient status from insufficiency back to adequate would result in benefits.

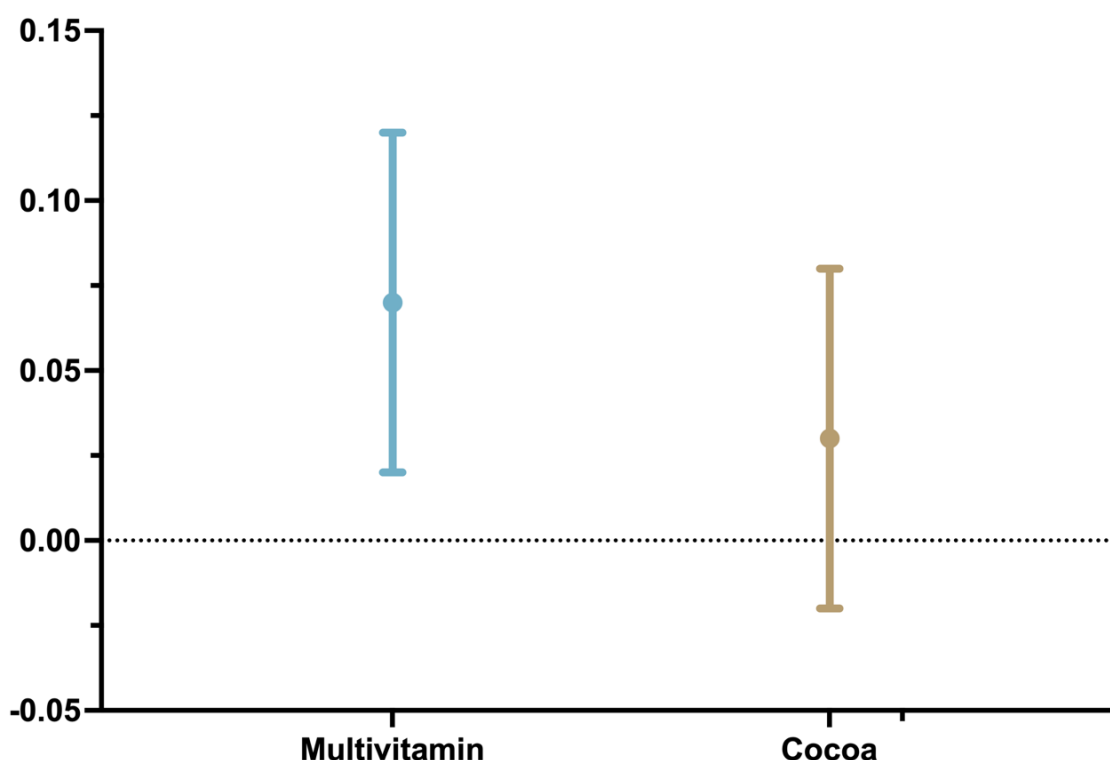
Relevance

The best way to view COSMOS-Mind is as two distinct interventions: the cocoa flavanol supplementation and the multivitamin supplementation.

The multivitamin itself contains several nutrients, in amounts of at least 100% the RDA in nutrients that have evidence of cognitive effects: vitamin E, vitamins B6, B9, and B12, and lutein. It is obviously impossible to determine which nutrients may have exerted benefits; the “exposure” here is the multivitamin formulation. The findings thus suggest that multivitamin supplementation, which contains added ingredients like lutein and lycopene, was effective at improving cognitive function and protecting against cognitive decline.

You might notice that even the placebo group increased, on average, in most outcomes; this may reflect the fact that this was, overall, quite a healthy, well-educated cohort of participants. Nevertheless, relative to the placebo groups, the treatment groups showed a greater change from baseline, which was statistically significant only in the multivitamin group.

The actual magnitude of difference between the two groups was relatively small; this is why it is important to think beyond “statistical significance” and look at the raw numbers. Let’s stack the primary outcomes next to each other; it is clearly advantage to the multivitamin. The effect in the cocoa group overall suggested some benefit, but did not approach the effect of the multivitamin on any outcome.



This is the largest, and longest, trial of cocoa flavanols to date. Based on that fact alone, it is sufficient to raise an amber light over whether the previous research in small studies conducted either over 1-2 hrs, a single day, or 8-weeks, is representative of the potential of cocoa flavanols to improve cognition in older adults.

Application to Practice

The findings of the parent COSMOS trial indicate that cocoa flavanols lower risk of CVD; the findings of COSMOS-Mind suggest no effect of cocoa flavanols on cognitive function. Given the “head and heart” analogy, this is, admittedly, a somewhat surprising finding.

Nevertheless, whatever further research may emerge for effects of cocoa flavanols, arguably a much more ecologically valid finding with more immediate practical application is the effects of the multivitamin. The product used was commercially available, showed good adherence and acceptability in the parent COSMOS RCT, and could be particularly useful in individuals with CVD risk factors and/or history of CVD.

This finding certainly challenges the “multivitamins are expensive pee” meme, and while that may be the case in younger adults with adequate dietary intake, it could be a relatively inexpensive insurance policy in older adults to protect the brain.

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