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NUTRITION

APIRL 2022

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Sesso HD, Manson JE, Aragaki AK, Rist PM, Johnson LG, Friedenberg G, Copeland T, Clar A, Mora S, Moorthy MV, Sarkissian A, Carrick WR, Anderson GL; COSMOS Research Group. Effect of cocoa flavanol supplementation for prevention of cardiovascular disease events: The COSMOS randomized clinical trial. Am J Clin Nutr. 2022:nqac055.

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

We love flavonoids. Especially those found in chocolate and wine, because #balance. Painful nutrition jokes aside, the (poly)phenols in cacao – flavan-3-ols and proanthocyanidins – are some of the most promising flavonoids for potential meaningful impacts on human health [(1,2)].

Like all flavonoids, what appears to be good for the head appears to be good for the heart. Several controlled interventions have found that cocoa flavanols improve acute cognition, an effect which may be due to increasing blood flow to the brain [(3,4)]. And improving blood flow may also be one reason why cocoa flavanols are associated with improved cardiovascular health [(1,2)].

Specifically, cocoa flavanols act through an enzyme, iNOS, which increases levels of nitric oxide, in turn improving vasodilation and lowering blood pressure [(1,2)]. There is also evidence that, in addition to lowering blood pressure and improving endothelial function, cocoa flavanols may improve blood cholesterol levels and other relevant cardiovascular disease markers, such as platelet aggregation [where blood cells adhere together at a site of injury] [(5)].

All of this is promising for these complex compounds. However, while the mechanisms are compelling and there is human outcome data in relation to intermediate risk factors, e.g., lower blood pressure, to date no large intervention study has had hospitalised or dead humans as an outcome. Does the Reaper fear Dairy Milk? This study found out…

The Study

The Cocoa Supplement and Multivitamin Outcomes Study [COSMOS] was conducted as a pragmatic* randomised controlled trial investigating the effects of a cocoa extract supplement and/or a multivitamin supplement in men and women over 60yrs of age.

21,444 participants were randomised to one of four groups:

- **Active** cocoa and **active** multivitamin
- **Active** cocoa and **placebo** multivitamin
- **Placebo** cocoa and **active** multivitamin
- **Placebo** cocoa and **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 have both placebo and active levels]. The dose of cocoa flavanols was 500mg and 80mg epicatechin per day, while the multivitamin was the U.S. commercial brand, Centrum Silver®.

Participants were required to not have any history of myocardial infarction, stroke, or cancer, within the 2yrs prior to entering the study Participants were provided with blinded calendar packages containing all capsules to take. The total duration of the study was 3.6yrs.

The primary outcome of the study was a composite of CVD events [including myocardial infarction (MI), stroke, CVD death, coronary artery bypass graft and percutaneous coronary intervention (CABG/PCI), unstable angina including hospitalization, carotid artery surgery, and peripheral artery surgery]; the secondary outcomes included CVD death and major CVD events [a tighter definition of CVD events confined to MI, stroke, and CVD death].

*Geek Box: Pragmatic RCTs

When we talk about "randomised controlled trials", it is often as if this term refers to a single type of design. And if you were to ask anyone who reads research what a "good" RCT looks like, they would likely list off certain methodological qualities, e.g., double-blinding and placebo-control. However, RCTs exist on a spectrum. The design characteristics we typically associate with RCTs – randomisation, double-blinding, placebo-control – and the related assumptions [e.g., independence of effects] are what are known as "explanatory RCTs". These RCT designs are aimed at high levels of internal validity, which are the design characteristics considered important to demonstrate efficacy, i.e., that the treatment A produces outcome B under ideal circumstances. In short, explanatory trials that test efficacy are asking, "does this work?" On the other end of the spectrum are what are known as "pragmatic RCTs". These trials are aimed at demonstrating external validity, which are the characteristics required to demonstrate effectiveness, i.e., how effective the treatment is in the real-world setting in which it will be applied. In short, pragmatic trials that test effectiveness are asking, "will this work to the same extent in real life?" Trials are not simply dichotomised along explanatory/efficacy – pragmatic/effectiveness lines, and so it is important to note that the word 'spectrum' here is not semantic. For example, a tightly controlled metabolic ward study may demonstrate that a certain diet, when specifically prepared and catered to participants, results in a particular outcome. Would that effect be observed, or observed to the same extent, if participants had to prepare and adhere to the diet in their day-to-day life? Such a study would not answer that question and would therefore be more to the purely explanatory end of the spectrum. However, a study in which the intervention was delivered through primary care where the participants knew they were receiving the treatment would be more to the pragmatic end of the spectrum, as it would be the exact "real world" scenario in which the treatment would be applied. Where a trial is designed to be a pragmatic RCT, factors like double-blinding are less of a concern to the methodological quality of the trial; single-blind or blinding of assessors may suffice. However, the quality of a pragmatic RCT will always be bolstered by taking extra steps to minimise bias. The Lyon-Diet Heart Study is a great example of a pragmatic RCT in nutrition; participants knew they were being asked to follow the intervention diet, but were unaware they were in a comparative trial. The researchers also kept the participant's doctors blinded to the fact that their patient was taking part in the trial, to avoid any undue changes to medications or routine care. Both explanatory and pragmatic RCTs have value for nutrition research, but with current knowledge the field would benefit from an emphasis on more pragmatic designs.

Results: The present study reported only on the effects of the cocoa supplement compared to the placebo [not the multivitamin results, which will be published at a later date]. The average age of participants was 72yrs, with women [74yrs] older than men [69yrs] on average. Other characteristics were similar at baseline. 42% of participants were taking statins, and 58% had high blood pressure, and 13% had type-2 diabetes. Over 3.6yrs [with 77,331 total person-years of follow-up], 570 participants died and 866 suffered a cardiovascular event.

- ***Primary Outcome – Total CVD Events*:** In the cocoa supplement group, there was a 10% [HR 0.90, 95% CI 0.78 to 1.02] lower risk of total CVD events compared to the placebo group, which was not statistically significant, i.e., the 95% CI crossed 1.0.
- ***Secondary Outcomes – Major CVD Events & CVD Death*:** In the cocoa supplement group, there was a significant 27% [HR 0.73, 95% CI 0.54 to 0.98] lower risk of CVD death compared to the placebo group. The cocoa supplement group also exhibited a significant 16% [HR, 0.84; 95% CI, 0.71, 0.99] lower risk of major CVD events.

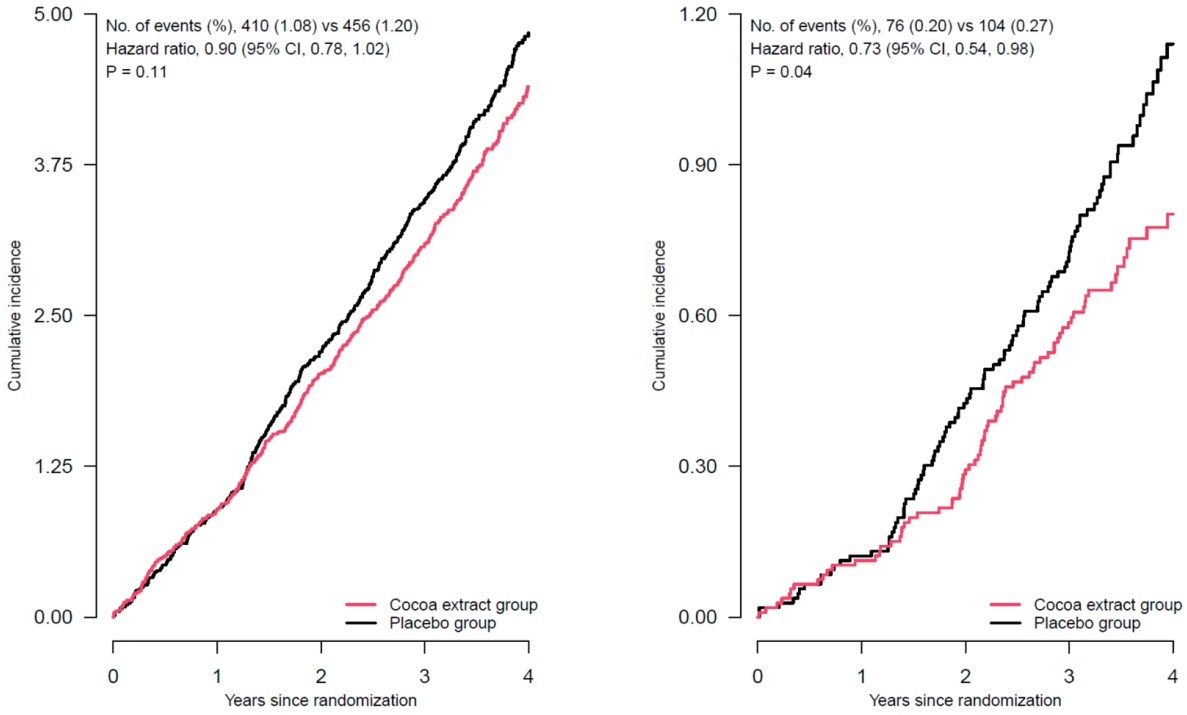

***Figure** from the paper illustrating [**left**] the difference in risk of experiencing the primary endpoint of total CVD events over ~4yrs [**X-axis**] between the intervention group [**red line**] and placebo group [**black line**]. And [**right**] illustrating the difference in risk for the secondary endpoint of CVD death between the cocoa intervention group and placebo group.*

- ***Analysis Excluding Non-Compliant Participants*:** For the primary outcome of total CVD events, confining the analysis to compliant participants resulted in a significant 15% [HR 0.85, 95% CI 0.72 to 0.99] lower risk compared to the placebo group. For the secondary outcomes, there was a 39% [HR, 0.61; 95% CI, 0.42 to 0.90] lower risk of death from CVD, and a 24% [HR 0.76, 95% CI 0.62 to 0.93] lower risk of major CVD events [more under ***Interesting Finding***, below].

The Critical Breakdown

Pros:

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. Although delivered in a free-living setting, the study was conducted with methodological rigour: 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; the study had a large sample size, particularly for a nutrition intervention. 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. Overall compliance was high; 83.1% and 84.2% compliance with the active cocoa treatment and placebo control, respectively, at the end of the intervention.

Cons:

The trial encountered some challenges [more under Key Characteristic, below] which may have lowered the level of power to detect stronger and more precise outcomes. While the sample size was large, there were a relatively low number of deaths and events which occurred during the follow-up period, some of which related to the Covid-19 pandemic. In terms of external validity, the study sample was 90% White ethnicity, 88% were third-level educated, and 55% never smoked; thus, there are some generalisability issues regarding wider context and application. While not a 'Con' *per se*, it is important to consider that the levels of cocoa flavanols and other (poly)phenols in the intervention supplement far exceed levels likely to be obtainable through diet alone.

Key Characteristic

Composite endpoints are a complex topic that are not without some debate. The major issue is that, by combining any number of endpoints into a composite – in this study "total CVD events" – a study can end up mixing endpoints that have both varying clinical relevance and reflect varying magnitudes of effect of the intervention. For example, if the treatment had a large effect on a less clinically relevant outcome, this would be reflected in the overall finding for the composite endpoint. Conversely, if the treatment has a beneficial effect on a more relevant clinical endpoint but little meaningful benefit on less relevant endpoints, this can weaken the ultimate strength of the finding.

And it appears that this latter issue may be at play in the present study. As the authors acknowledge in their design paper [6] [and indeed in the published paper of the present Deepdive], the original submitted primary endpoint was intended to be a composite of MI, stroke, coronary revascularization, and cardiovascular death. However, the Covid-19 pandemic resulted in less reported CVD event rates, while the study also recruited younger women – although the average age was 74yrs, the recruitment expanded to include younger women who have lower CVD risk and event rates – and 42% of participants were taking statins, which would also lower risk.

As a result of these factors, the original composite endpoint may have resulted in weakened strength of the outcome. The investigators obtained approval to expand the primary endpoint to include carotid artery surgery, peripheral artery surgery, and unstable angina requiring hospitalization. In secondary analyses which examined the effects of each endpoint in isolation, you can see [circled in red in the **Figure**, below] that these findings were purely noise; confidence intervals as wide as a wizards sleeve.

However, if we look at the composite secondary endpoint of "major CVD events" [MI, stroke, and CVD death], which closely reflects the original intended primary endpoint before it was expanded, there was a significant 16% lower risk from the cocoa extract treatment. This finding was strengthened to a 24% lower risk when omitting participants with low compliance [more under ***Interesting Finding***, below].

Thus, we are left with an open question: what would the strength of the findings have been if the study did not encounter the challenges of low event rates in the study group due to a combination of the above-mentioned factors? The findings for major CVD events should provide sufficient fodder for a funding source to open the wallet for another intervention.

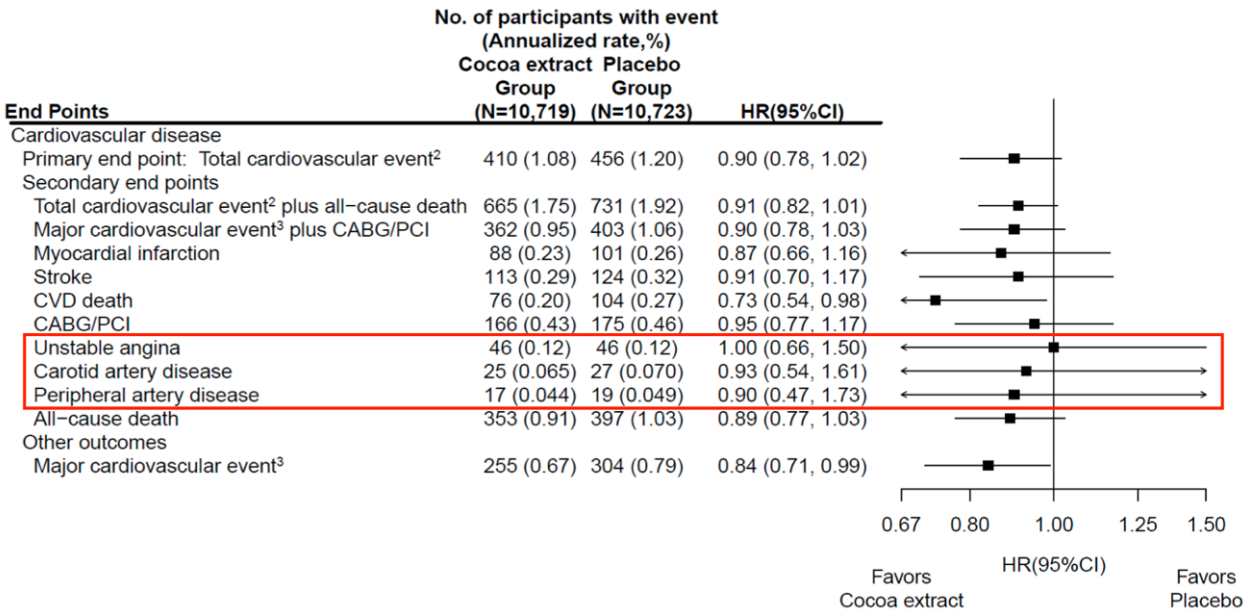

Figure *from the paper with the endpoints which were added to the composite primary endpoint after the initiation of the study. As you can see from the confidence interval arms for each of these endpoints, the findings are basically noise. However, if you look at the very bottom at "major cardiovascular events", this is a more discernible outcome as far as direction of effect. It will be interesting to see this intervention replicated with a more tightly defined composite primary endpoint.*

Interesting Finding

The differences in the strength of the findings were clearly mediated by the level of compliance with the study protocol. The study conducted what is known as a "per protocol analysis", which is where the analysis is confined to participants who completed the study having complied with the trial protocols.

In the present study, participants were deemed non-compliant from the first time they either reported missing >8 days of cocoa extract capsules per month, reported taking personal non-study cocoa extract products, or did not respond to the semi-annual questionnaire administered to participants during follow-up.

And in this per protocol analysis, the results of each outcome [illustrated in the ***Figure***, below] were strengthened in their estimate of effect. In the present study, the compliance levels included in this analysis were balance between groups - 78.1% and 79.3% in the treatment and control groups, respectively – and compliance remained high overall at the end of the study.

Nevertheless, per protocol analyses must be taken with a pinch of salt due to the potential to introduce bias into the findings [e.g., by resulting in very highly motivated participants disproportionately in the intervention group].

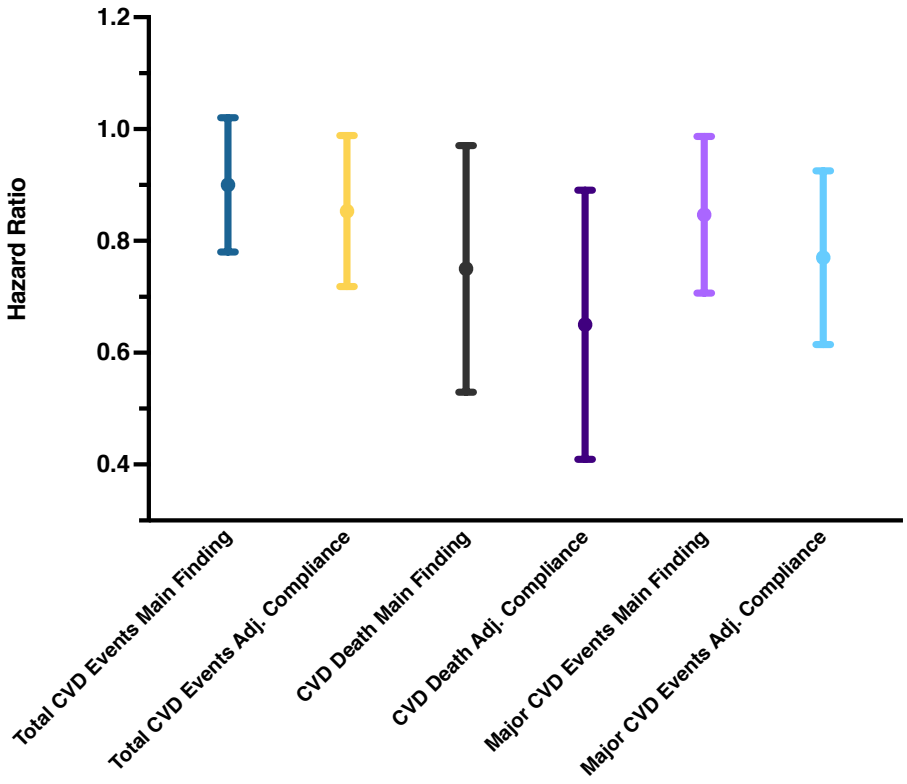

Figure *illustrating the hazard ratio [**circle** in each bar] and accompanying 95% confidence intervals [**top** and **bottom** arms of each bar] for the main primary endpoint [total CVD events] and two secondary endpoints [CVD death and major CVD events (MI, stroke, and CVD death combined)]. "Adj. Compliance" indicates the per protocol analysis excluding non-compliant participants. The red-shaded area above 1.0 indicates increased risk, while the green shaded area below 1.0 indicates reduced risk.*

Relevance

It is important to bear in mind that for the rigour of the present study, and the fact that it is the first-in-class as a longer-term intervention testing the effects of a high-dose cocoa (poly)phenol extract on clinical endpoints, the beneficial effect is largely reflected in secondary outcomes. That said, while the primary outcome was not "statistically significant", the direction of effect is evident.

The modest effect size for the primary outcome – a 10% lower risk – should be considered in the context of the inclusion of several less relevant clinical endpoints into what was ultimately a more wishy-washy composite primary outcome. If we look closer at some of the more rigorous endpoints – CVD death in particular – the signal-to-noise ratio in these data are strong, particularly for a nutritional treatment.

Open questions, however, remain. If the trial was not disrupted by Covid and recruiting younger, lower risk participants, what would the effect have been? If the more robust endpoint of major CVD events [which included CVD death] had remained the primary endpoint, would the effect size have been larger in a primary analysis?

While we must be cautious in interpreting secondary endpoints [due to potentially less statistical power] and "per protocol" analyses [due to potential bias], based on the outcome for major CVD events [remember: MI, stroke, and CVD death], there is sufficient evidence from this study to warrant repeating an intervention with high-dose cocoa flavanol extract supplementation in a future large study.

Finally, it is important to think about biological plausibility of the findings: blood pressure-lowering effects, anti-inflammatory effects, improving vascular function and protection of the vascular endothelium, bolstering endogenous antioxidant capacity, and improving blood cholesterol profiles, have all been demonstrated for cocoa flavanols [7]. These effects have been shown in human intervention studies, mostly short-term of <4-weeks duration, with doses similar to the levels of cocoa flavanols and epicatechins used in the present study [7]. Thus, there is congruence between the benefits of cocoa flavanols on cardiovascular risk factors observed in short-term interventions and the lower CVD risk found over the longer-term in the present study.

Application to Practice

For wider generalisability, it is important to remind ourselves of the characteristics of the study sample; older, well-educated, and a degree of baseline risk reflected in prevalence of hypertension and statin treatment. The question we are left to ponder is whether there is any applicability of these findings to a younger, healthy population group?

In that regard, it is encouraging that for flavonoids – including cocoa flavanols specifically – the effects observed in higher-risk populations have tended to be replicated in younger, healthy participants [7–11]. This is encouraging as it may mean that regular intake of flavonoid-rich foods may exert prophylactic effects over time, particularly if consumed regularly from earlier in life.

Depending on the method of quantifying cocoa flavanol content, and the cocoa content of the type of, chocolate it could take 1kg of chocolate to obtain levels used in the present study. However, benefits on blood pressure have been demonstrated with as little as 30mg cocoa flavanols, up to 240mg, levels which could easily be obtained with 20-40g ~80% cacao dark chocolate [2,5]. The research does clearly show that the higher the cacao content of the chocolate, the greater the flavanol, epicatechin, and total (poly)phenol content. The important take-home point is that, from a general health perspective, benefits of cocoa flavanols may be obtained through foods more readily consumed in a habitual diet.

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