



Cognitive Vitality Reports[®] are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-indevelopment, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Сосоа

Evidence Summary

Cocoa powder high in flavanols may confer cardiovascular benefit, and cocoa flavanols may improve cognition in individuals who have low flavanol levels. No safety concerns have been identified.

Neuroprotective Benefit: While cocoa flavanols can provide some cardiovascular benefits that can indirectly improve brain health, large randomized controlled studies have not found cognitive benefits of cocoa flavanols.

Aging and related health concerns: The strongest evidence for health benefit with cocoa flavanols is for cardiovascular health; they appear to improve blood pressure and may improve cardiovascular outcomes, particularly in hypertensive individuals.

Safety: Cocoa supplementation has been tested in large randomized controlled trials and no serious safety concerns have been identified in these trials. It is best taken with food. Cocoa source should be checked for lead and cadmium levels.

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Availability : In food, as a supplement, or in a powder	Dose : Ideal dose unknown. Benefits, if any, typically seen between 500 -750 mg flavonoids, taken daily, orally, with at least 50 mg epicatechin.	There are a variety of cocoa flavanols. Epicatechins are one of the most studied cocoa flavanols. <u>(-)-epicatechin</u>	
Half-life: Varies on flavanol; epicatechin half life is approximately 2.5 hours	BBB : Many cocoa flavanols, including epicatechin, are BBB penetrant	C ₁₅ H ₁₅ O ₆ 290.27 Source:	H ₀ H ₀ H ₀ H ₀ H ₀ H
Clinical trials: The largest clinical trial of cocoa flavanols enrolled 21,442 participants.	Observational studies : The largest observational study of chocolate consumption included 84,709 people.	PubChem	но

What is it?

The cocoa bean, also called the cacao bean, is the processed seed of the Theobroma cacao tree. Cocoa beans are used to generate cocoa solids (eg. cocoa powder) and cocoa butter, which are used in turn to create chocolate as well as other foods like mole sauce. Cocoa powder contains methylxanthines (caffeine and theobromine) and flavanols, a subclass of flavonoids that includes (-)-epicatechin and procyanidins. For this review, epicatechin will be used to denote (-)-epicatechin, unless otherwise noted.

Flavanols or Flavon-3-ols, especially epicatechins, are often assumed to be the active ingredient in chocolate and cocoa for health, but cocoa is not the primary source of flavanols in our diet. For example, one recent study concluded that Europeans get most of their flavanols from tea, then pome fruits (eg. apples, pears), then berries and small fruits, followed by cocoa beans and related products consisting of 3% of the dietary sources of flavanols (Vogiatzoglou et al., 2014). The flavanol content in cocoa-related foods varies substantially depending on the geographic source of the beans and as well as how they were processed and stored.

Cocoa flavanols have been proposed to have a variety of beneficial functions, including improving cardiovascular health through actions like increasing vasodilation, blood flow and angiogenesis;

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decreasing inflammation and oxidative stress; modulating insulin sensitivity; and improving cognitive function (<u>Barrera-Reyes et al., 2020</u>).

Neuroprotective Benefit: While cocoa flavanols can provide some cardiovascular benefits that can indirectly improve brain health, large randomized controlled studies have not found cognitive benefits of cocoa flavanols.

Types of evidence:

- 1 systematic review
- 15 randomized controlled clinical trials
- 5 observational studies
- 2 open label trials
- 1 review
- 3 laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

Data from randomized controlled trials and observational studies report mixed results of cocoa flavanols.

A 2020 paper systematically reviewed randomized controlled trials that enrolled healthy adults and treated with cocoa flavanols alone. Some of the studies were placebo controlled, and some compared low vs. high cocoa flavanol supplements. The 12 included trials enrolled a total of 657 participants, and all were 12 weeks or less in duration. The review indicated that cocoa flavanol doses of 500 – 750 mg daily, containing at least 50 mg of epicatechins, were more often associated with cognitive benefit (Barrera-Reyes et al., 2020).

Short clinical trials up to 8 weeks duration have had mixed results but suggest that chocolate or cocoa might improve some but not most aspects of cognitive function. Other trials in elderly patients and younger people have been very mixed, per the conclusions of a systematic review, with short-term cognitive improvement sometimes but rarely seen along with increased cerebral blood flow (<u>Scholey & Owen, 2013</u>).

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One explanation for varied results is the type of treatment or specific outcome measure. Cocoa and chocolate products vary extensively in their flavanol content. If the flavanols are the active ingredients, this variability might explain why the observational data is mixed from null (Vercambre et al., 2013) to benefit (Nurk et al., 2009, Sun et al., 2023). However, clinical trials that compared high vs low flavanol cocoa drinks are also mixed. One trial reported benefit specifically from flavanol-enriched cocoa (Brickman et al., 2014). A follow up study from the same group seeking to replicate their results also found some cognitive benefit in certain measures of hippocampal memory with flavanol supplementation, particularly in subjects with low baseline flavanol intake, though their overall study suffered from technical issues in their primary endpoint (Sloan et al., 2021). On the other hand, other randomized controlled trials have not identified cognitive benefits (Crews et al., 2008). Baseline health might also affect the results.

The <u>CO</u>coa <u>Supplement and Multivitamin Outcomes Study</u> (COSMOS) is a US-wide trial that randomized 21,449 people to study the effects of long-term cocoa and / or multivitamin supplementation on a variety of health outcomes, including cardiovascular health, cancer, and cognitive function, among others. Enrollees were men 60 years and older and women 65 years and older, with no history of myocardial infarction or stroke, no history of cancer in the past two years besides non-melanoma skin cancer, no serious illness, and not taking cocoa or other vitamin/mineral supplements. Patients who were willing to stop supplement intake for the trial were able to enroll.

COSMOS-Mind is an ancillary study that focuses on cognition. This portion of COSMOS enrolled 2,262 patients from the parent COSMOS study. Participants took a supplement daily for three years, based on their randomization group: placebo; 500 mg cocoa flavanols (Mars, including 80 mg (-)-epicatechins and modest amounts of theobromine (~50 mg/day) and caffeine (~15 mg/day); a multivitamin (Centrum Silver); or both cocoa flavanols and the multivitamin. Researchers administered a standardized telephone cognitive battery at baseline and then once annually for the 3 years of the study. The primary outcome was the global cognitive score.

<u>Baker et al., 2022</u> detailed the results of COSMOS-Mind. Of the 2,262 participants, 92% completed the baseline and at least one annual cognitive testing timepoint. The authors found no effect of cocoa supplementation on cognitive function as compared to placebo (mean z-score = 0.03; 95% Cl 0.02 to 0.08; P = 0.28). The authors did, however, find a cognitive benefit of multivitamin supplementation as compared to placebo (mean z = 0.07; 95% Cl 0.02 to 0.12; P = 0.007). This cognitive benefit was more pronounced in participants with a history of cardiovascular disease (no history: z = 0.06; 95% Cl 0.01 to

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0.11; history: z = 0.14; 95% CI 0.02 to 0.31), though a sensitivity analysis indicated that the multivitamin still provided benefit to those without history of cardiovascular disease.

COSMOS-Web was another ancillary study of COSMOS. This substudy enrolled 3,960 subjects from the parent study and utilized yearly web-based testing to see if and how cognitive function changed over the course of the 3-year trial in participants randomized to cocoa supplementation compared to the placebo group. A total of 3.562 participants completed at least one yearly follow-up cognitive assessment. The outcomes of the study included different assessments of cognition and memory.

Like COSMOS-Mind, COSMOS-Web did not find an overall improvement in cognition or memory in participants in the cocoa group as compared to those in the placebo group. However, in pre-specified secondary endpoint analyses, the authors stratified their participants by habitual diet quality, which correlates with dietary intake of flavanol-rich foods, or by urinary gVLM levels, which is a metabolite of flavanols and therefore a biomarker of flavanol levels. The researchers found that low habitual diet scores and low gVLM scores were associated with worse baseline memory. In the subjects with low habitual diet scores or low gVLM, cocoa supplementation significantly improved hippocampal-dependent memory as compared to subjects who received placebo. These effects were apparent at the 1-year timepoint and was sustained over the rest of the trial. Increases in gVLM levels were also associated with improved memory. The results of this trial suggest that cocoa supplementation may have cognitive benefits specifically for those who have lower than average levels of flavanols (Brickman et al., 2023).

There are several possible reasons for the discrepancy between the earlier positive results and some of the null results of COSMOS-Mind and COSMOS-Web. While COSMOS-Mind included doses of both cocoa flavanols and epicatechins that appear to be beneficial, it is possible they still were not the correct dose. The COSMOS-Mind study was also much longer than previous trials. It is possible that cocoa flavanols provide an acute benefit rather than a long-lasting one, though why that would be the case is not clear. It is possible that flavanol supplementation does provide a cognitive benefit, but only when the individual does not have sufficient flavanol levels from dietary intake. It is also possible that the COSMOS trials reflect an underlying biological truth that the prior, smaller studies were not powered enough to identify.

In terms of observational data, cocoa flavanol intake has been associated with reduced incidence of and death from dementia. An observational study of 84,709 postmenopausal women found that compared

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to no chocolate consumption, some levels of moderate chocolate consumption was associated with reduced death from dementia (HR=0.89; 95% CI 0.80 to 0.99, 4-6 servings per week) (<u>Sun et al., 2023</u>).

Despite the mixed and limited evidence for cognitive benefit, the overall body of research suggests that long-term treatment might protect against cognitive decline and neurodegeneration through cardiovascular and metabolic health, inflammation, and oxidative stress (discussed in the aging section below).

Human research to suggest benefits to patients with dementia:

One trial in patients with mild cognitive impairment reported that a high-dose flavanol cocoa had no overall effect on MMSE cognitive scores but improved scores on 2 cognitive tests. The treatment also improved a variety of markers of health related to insulin resistance, blood pressure, and oxidative stress (the CoCoA study on 520-990mg/d cocoa flavanols) (Desideri et al., 2012). Another trial reported that high-flavanol cocoa (900mg flavanols + 138 mg epicatechin/d) improved performance on a cognitive task vulnerable to brain aging but no benefit on a cognitive task vulnerable to early stages of Alzheimer's disease (Brickman et al., 2014; Cognitive Vitality report).

A 2023 study tested the effects of cocoa flavanols and omega-3 fatty acids on cognitive function and brain structure in adults with subjective memory complaints or mild cognitive impairment. The study randomized 259 adults to one of two groups: a placebo group and an intervention group that received 500 mg flavanols (Abbott Nutrition, including 80 mg epicatechins) and omega-3 capsules that contained a total of 1.1 g DHA and 0.4 g EPA daily (Abbott Nutrition). In total, 197 participants completed the 1-year trial. Adherence was confirmed through plasma DHA and EPA levels as well as with urinary flavanol metabolite levels. The authors found no benefit of the intervention in terms of cognitive function or brain structure (Vauzour et al., 2023).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

As reviewed by <u>Barrera-Reyes et al., 2020</u> and <u>Lalonde & Strazielle, 2023</u>, there are a number of potential mechanism of action of cocoa flavanols such as epicatechin. Cocoa flavanols are thought to improve peripheral and cerebral blood flow, which improves brain health. Flavanols may also directly modulate proteins that are involved in neurogenesis, neuronal function, and synaptic connectivity; for instance, flavanols may increase levels of BDNF. Preclinical studies have reported that cocoa flavanol administration reduced A^β levels, mitigated A^β oligomerization, and tau hyperphosphorylation. Cocoa

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flavanols may also play neuroprotective roles through their anti-inflammatory and anti-oxidant functions.

Cocoa flavanols are metabolized by the gut microbiome, and some of those metabolites are bioactive and could play a neuroprotective role. The mechanistic role of these metabolites is still a very new and exploratory area of research.

APOE4 interactions:

It is not clear whether APOE4 carriers have differential responses to cocoa flavanols.

Aging and related health concerns: The strongest evidence for health benefit with cocoa flavanols is for cardiovascular health; they appear to improve blood pressure and may improve cardiovascular outcomes, particularly in hypertensive individuals.

Types of evidence:

- 1 Cochrane meta-analysis
- 3 meta-analyses and/or systematic reviews
- 3 randomized controlled clinical trials
- 10 observational studies
- 1 open label trial
- 1 review
- 4 laboratory studies

A number of studies have investigated whether cocoa flavanols have any impact on aging or related health concerns. The evidence for improving cardiovascular health, particularly blood pressure, appears to be the strongest.

Aging/mortality: UNCLEAR

A large observational trial of 84,709 postmenopausal women found that compared to no chocolate consumption, moderate chocolate consumption was associated with reduced all-cause mortality

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(HR=0.93; 95% CI 0.89 to 0.96, 1 to 3 servings per week) along with death from cardiovascular disease and dementia as discussed in the cardiovascular and dementia sections, respectively (<u>Sun et al., 2023</u>).

One prospective cohort in 470 elderly men reported that highest cocoa intake (quartiles) had lower risk all-cause mortality (RR=0.53; 95% CI 0.39 to 0.72) over 15 years follow-up (<u>Buijsse et al., 2006</u>). One rat study reported increased lifespan with 12 months treatment of 24 mg/kg/d cocoa polyphenolic extract (Acticoa powder) (<u>Bisson et al., 2008</u>). One fruit fly study reported increased lifespan but also possible pro-oxidant effects in conditions of extreme oxidative stress (<u>Bahadorani & Hilliker, 2008</u>).

Large randomized controlled studies such as the COSMOS trial have not found an overall mortality benefit of cocoa use, but this may be due to the relatively short follow up period of 3 years (<u>Sesso et al.</u>, <u>2022</u>).

Aging function: UNCLEAR

One randomized trial of combined group exercise, oral care, chocolate, and supplements in nursing home residents reported no effect on cognitive performance but protection from social and physical decline (<u>Bahadorani & Hilliker, 2008</u>).

Insulin resistance: UNCLEAR

A 2012 meta-analysis of short-term RCTs suggested decreased serum insulin but minimal effects on fasting glucose levels (<u>Hooper et al., 2012</u>). A 2012 RCT in mild cognitive impairment reported that improved insulin resistance accounted for 40% of the variability in the observed benefits to cognitive function (<u>Desideri et al., 2012</u>).

Inflammation and Oxidative Stress: UNCLEAR

Minimal evidence but 1 cohort study in healthy Italians (<u>di Giuseppe, et al., 2008</u>) and 1 RCT in Iranian diabetic patients (<u>Parsaeyan et al., 2014</u>) reported decreased biomarkers of inflammation like CRP while a small RCT reported no benefit of cocoa versus green tea on CRP or IL-6 (<u>Stote et al., 2012</u>).

Small RCTs suggest that cocoa flavanols can reduce oxidative damage (<u>Desideri et al., 2012</u>, <u>Stote et al.,</u> <u>2012</u>, and others) although effects are not consistent (eg. <u>Spadafranca et al., 2010</u>)

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Cardiovascular benefits: BENEFIT

One prospective cohort in 470 elderly men reported that highest cocoa intake (quartiles) had lower risk of cardiovascular-related mortality (RR=0.50; 95% CI 0.32 to 0.78), and lower systolic & diastolic blood pressure, over 15 years follow-up (Buijsse et al., 2006). A 2023 observational study of 84,709 postmenopausal women found that compared to no chocolate consumption, moderate chocolate consumption (1 to 3 servings per week) was associated with reduced cardiovascular disease death (HR=0.88; 95% CI 0.82 to 0.95) (Sun et al., 2023).

One meta-analysis of 42 small short RCTs suggests that chocolate or cocoa can reduce blood pressure (diastolic and arterial) and improve flow-mediated dilation (<u>Hooper et al., 2012</u>). One meta-analysis of 10 trials of 2-12 weeks duration suggests dark chocolate/cocoa reduces LDL and total cholesterol but does not consistently affect HDL or triglyceride levels (<u>Tokede et al., 2011</u>). For longer intake, RCTs are not available but a 2011 meta-analysis concluded that 5 of 7 observational studies report a lower risk of cardiovascular disease (RR=0.63; 95% CI 0.44 to 0.90) and stroke (RR=0.71) when highest intake of chocolate is compared to lowest intake (by quartiles). More recent cohort studies report decreased risk of cardiovascular endpoints including heart failure (<u>Petrone et al., 2014</u>) and calcified atherosclerotic plaque (<u>Djoussé et al., 2011</u>) with the former specific to people with BMI below 25.

A 2020 study from Ottaviani and colleagues investigated the relationship between levels of flavanol biomarkers and blood pressure in 25,612 subjects, all aged 40 to 75 years at enrollment, in the prospective study European Prospective Investigation into Cancer and Nutrition (EPIC) in the Norwalk cohort. Participants were not given supplements; their flavanol levels were from dietary intake, particularly tea, as tea is a rich source of flavanol and the study took place in England. The investigators looked at whether urinary levels of the flavanol biomarkers vGLM and SREM were associated with blood pressure and cardiovascular risk factors. They found that higher vGLM and SREM levels were associated with significantly lower systolic and diastolic blood pressure, and inversely associated with blood lipids. The association was particularly strong in older or more hypertensive individuals. The reduction in blood pressure was comparable to that observed with a Mediterranean diet in the PREDIMED trial or moderate reduction in salt intake in the DASH Sodium trial (Ottaviani et al., 2020).

While the work from Ottaviani and colleagues was an observational study of diet and metabolites, a Cochrane meta-analysis of randomized controlled trials of 1804 patients, testing cocoa or chocolate with

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an average dose of 670 mg of flavanols, found moderate-quality evidence of a small but significant decrease in blood pressure in groups treated with cocoa flavanols. This effect tended to be stronger in hypertensive participants (<u>Ried et al., 2017</u>).

As mentioned in the section on 'Human research to suggest prevention of dementia', the COcoa Supplement and Multivitamin Outcomes (COSMOS) is a US-wide trial that randomized 21,449 people to study the effects of long-term cocoa and/or multivitamin supplementation on a variety of health outcomes, including cardiovascular health, cancer, and cognitive function, among others. Enrollees were men 60 years and older and women 65 years and older, with no history of myocardial infarction or stroke, no history of cancer in the past two years besides non-melanoma skin cancer, no serious illness, and not taking cocoa or other vitamin/mineral supplements. Patients who were willing to stop supplement intake for the trial were able to enroll. Adherence to the trial was assessed through assessment of gVLM, a urinary biomarker of flavanol intake.

The main study looked at whether cocoa supplementation and/or multivitamin use decreased total cardiovascular disease as compared to placebo. The average follow-up duration was 3.6 years. The authors did not find a significant difference between the groups in terms of total cardiovascular events (HR=0.90; 95% CI: 0.78 to 1.02; P = 0.11). In a pre-specified analysis that controlled for adherence to the trial in all groups, cocoa supplementation trended more towards reduction of cardiovascular events as compared to the placebo (HR=0.85; 95% CI 0.72 to 0.99). There was a significant 27% decrease in cardiovascular death in the cocoa supplement group as compared to placebo (HR=0.73; 95% CI 0.54 to 0.98). The authors caveat that their analyses were not controlled for multiple testing and that their significant outcome was a secondary outcome (Sesso et al., 2022).

Safety: Cocoa supplementation has been tested in large randomized controlled trials and no serious safety concerns have been identified in these trials. Best taken with food; nausea has been reported. Cocoa source should be checked for lead and cadmium levels.

Types of evidence:

- 1 Cochrane meta-analysis
- 3 clinical trials
- 3 laboratory studies

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The safety concerns of chocolate, cocoa, and cocoa flavanol supplements are few and mainly related to either the caffeine content or the sugars and saturated fat common to chocolate and related foods. On the other hand, the high-dose flavanol supplements in use today are new to our diets, with little long-term information collected either through long-term broad public use or through research.

A 2017 Cochrane meta-analysis found that cocoa products were 'highly tolerable', with moderate quality evidence for more gastrointestinal complaints and nausea adverse events in cocoa groups compared to control groups (1% vs. 0.4%, respectively) (<u>Ried et al., 2017</u>).

The COSMOS studies randomized 21,442 patients to one of four groups: placebo, 500 mg of cocoa flavanols, a multivitamin, or both the cocoa supplement and the multivitamin. The participants took their assigned study treatment daily for 3 years. The study found no safety concerns. COSMOS did find that participants in the cocoa extract group were significantly more likely to report nausea (HR=1.06; 95% CI: 1.02 to 1.11). However, this may have been exacerbated by noncompliance with study guidelines that recommend taking the cocoa supplement with food (Sesso et al., 2022).

Interestingly, participants in the cocoa supplementation group were less likely to report flu-like symptoms and headache than the placebo group (HR=0.95; 95% CI: 0.91 to 0.99 for both adverse event) and much less likely to report experiencing migraines (HR=0.85; 95% CI: 0.78 to 0.93) (<u>Sesso et al.,</u> 2022). The substudy COSMOS-MIND similarly reported that they observed no safety concerns (<u>Baker et al., 2022</u>).

There have been reports of high levels of lead and cadmium in certain brands of dark chocolate or other cocoa products, including cocoa powder. This is a particular concern for pregnant people and children, though high levels of heavy metals are best avoided for any population.

Dark chocolate tends to have higher lead and cadmium concentrations than milk chocolate.

Drug interactions:

Cocoa flavanols are thought to lower blood pressure, and some preclinical evidence indicates that cocoa flavanols may have ACE-inhibitory effects. Individuals who are at risk of low blood pressure or use antihypertensives, including ACE inhibitors, may want to monitor their blood pressure accordingly (WebMD).

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Cocoa products typically contain <u>caffeine</u> which may interact with a variety of medications (WebMD for <u>Cocoa</u>, WebMD for <u>Caffeine</u>).

Research underway:

There are around 50 ongoing trials involving cocoa that are registered with clinicaltrials.gov. The indications include type 2 diabetes, metabolic syndromes including obesity, cardiovascular disease and depression. There are also three ongoing trials that involve aging, cognitive function, or dementia.

<u>NCT05343611</u> is an RCT enrolling patients with mild cognitive impairment or mild dementia and testing whether supplementation with cocoa and vitamin E can help prevent protein-energy malnutrition and muscle wasting. Participants will also be on a protein-rich diet and physical exercise program. The investigators will assess parameters of metabolism and cognition, including muscle mass and strength, cognitive function, cortisol, mitochondrial metabolism, and inflammation. The study aims to screen 150 patients with the goal of having 102 patients complete the trial, split equally between a placebo group, a group that will receive 30 g/day of dark chocolate containing 500 mg total polyphenols, including 60 mg epicatechin, and a third group that will receive the same 30 g/day of dark chocolate and also 100 mg of vitamin E daily. The intervention will last for 6 months.

<u>NCT03723694</u> is an RCT examining the effects of a cocoa-derived dietary flavanol on cognitive function and in markers of inflammation in healthy adults aged 50-69. The study plans to enroll 146 participants. The participants will receive either placebo or 650 mg of cocoa flavanols. The primary outcome is inflammation as assessed by plasma levels of HMGB1; secondary outcomes include measures of cognition and levels of TNFα and NFkB.

<u>NCT05510375</u> is an ancillary study of COSMOS participants, discussed in the neuroprotection section. COSMOS recruited men over 60 and women over 65 and randomized participants to one of four groups. In these groups, participants received either: placebo, daily cocoa extract containing 500 mg of flavanols included 80 mg of epicatechins, a standard multivitamin, or both cocoa extract and the multivitamin. The overall COSMOS study enrolled 21,442 participants. This sub-study is examining whether the daily supplement(s) had any effect on epigenetic aging or inflammaging, as measured by several inflammatory markers that are associated with aging. Secondary outcomes include measures such as blood pressure and BMI.

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Search terms:

Pubmed, Google: cocoa and/or cocoa flavanols +

• Dementia, APOE4, AD, cardiovascular disease, blood pressure

Websites visited for cocoa and/or cocoa flavanols:

- <u>Clinicaltrials.gov</u>
- Examine.com
- Geroprotectors
- Drugs.com
- WebMD.com
- <u>PubChem</u> (epicatechins)
- <u>Labdoor.com</u> (Limited information)
- <u>ConsumerLab.com</u>

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