



**The *CO*coa Supplement and *M*ultivitamin *O*utcomes Study (COSMOS):
A Randomized Trial of Cocoa Flavanols and Multivitamins
in the Prevention of CVD and Cancer**

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WHI Investigators Meeting

May 7, 2015

Rationale for the COSMOS Trial

- **Emerging evidence that cocoa flavanols (CF) reduce risk of cardiovascular disease (CVD) and that multivitamins (MV) may reduce risk of cancer.**
 - **No previous large-scale randomized clinical trials have been conducted in either men or women for CF or in women for MV.**
 - **A prevention trial among women in WHI and men among VITAL respondents is highly cost-effective.**
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COSMOS Is Not a Chocolate Study (Sorry!)

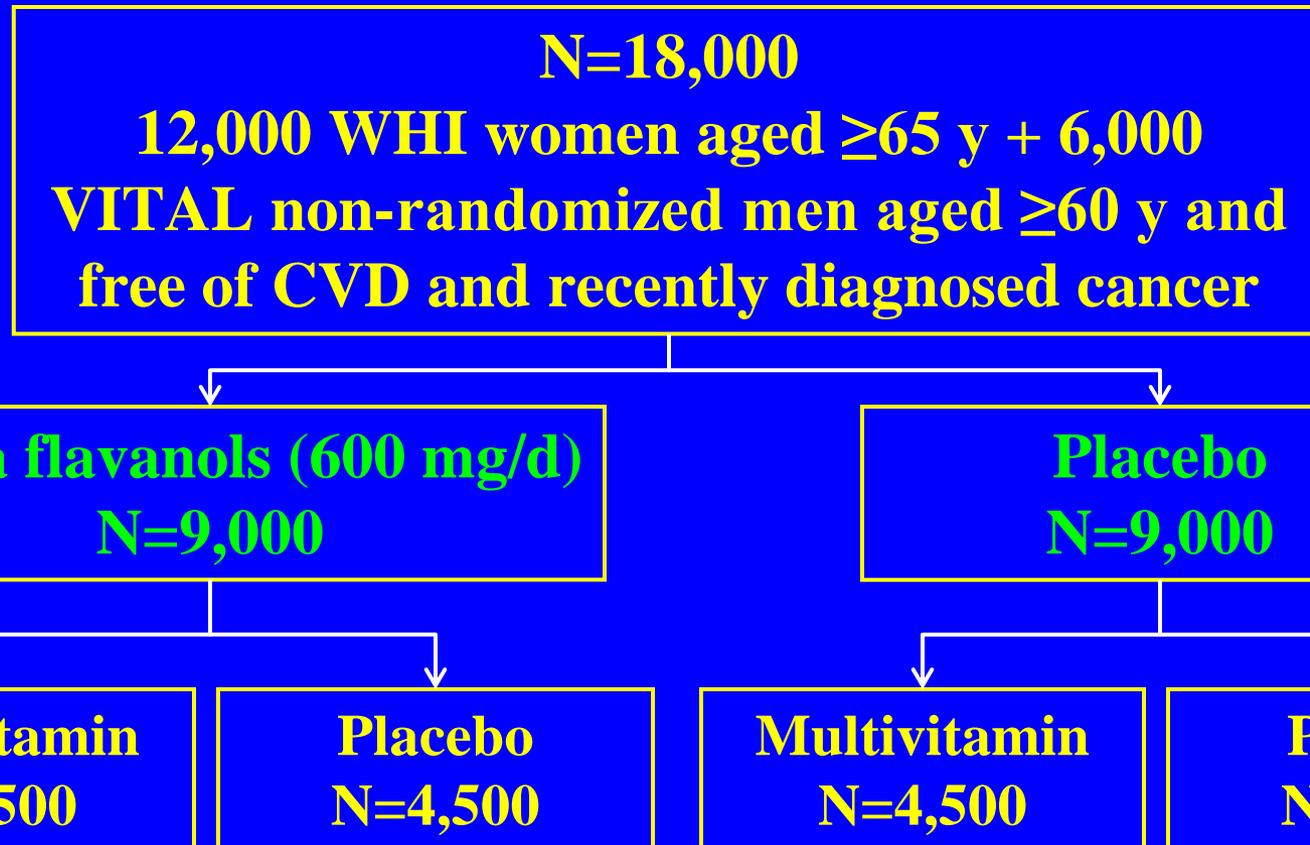


Chocolate Candy



COSMOS

COSMOS Trial Design



Mean Treatment Period = 4.0 years.

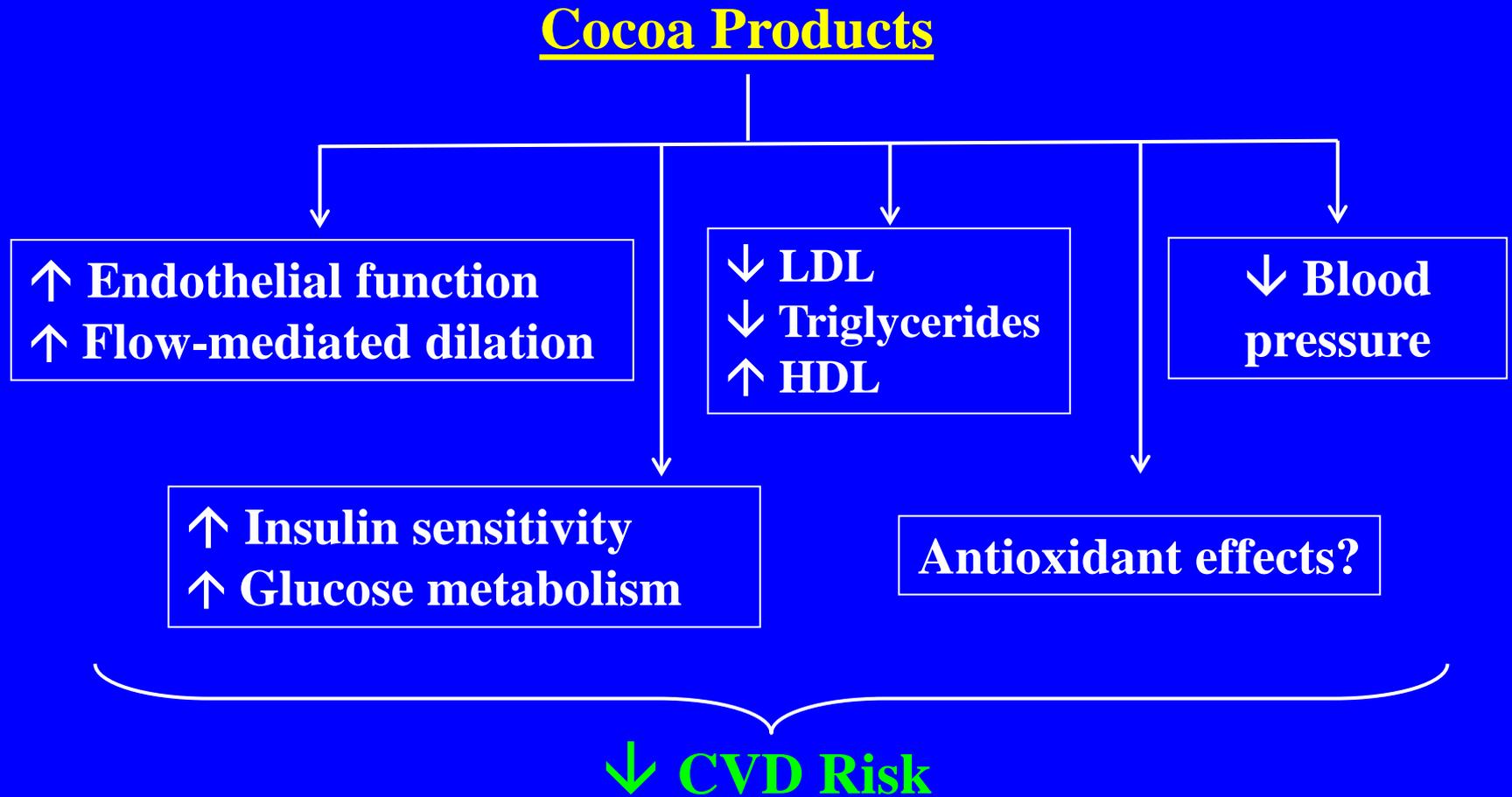
Primary Outcomes: Major cardiovascular events (MI, stroke, CVD death, and coronary revascularization) and total cancer (excluding non-melanoma skin cancer).

Baseline Blood Collection in ~4000 participants; F/U samples in 2000.

Cocoa

- **The cocoa bean comes from the cacao plant, Theobroma cacao, which when processed forms cocoa and chocolate.**
 - **Beneficial effects of cocoa have been attributed to its high polyphenol and flavonoid content:**
 - **Catechins**
 - **Epicatechins**
 - **Procyanidins**
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Multiple Mechanisms Through Which Cocoa Products May Lower the Risk of CVD

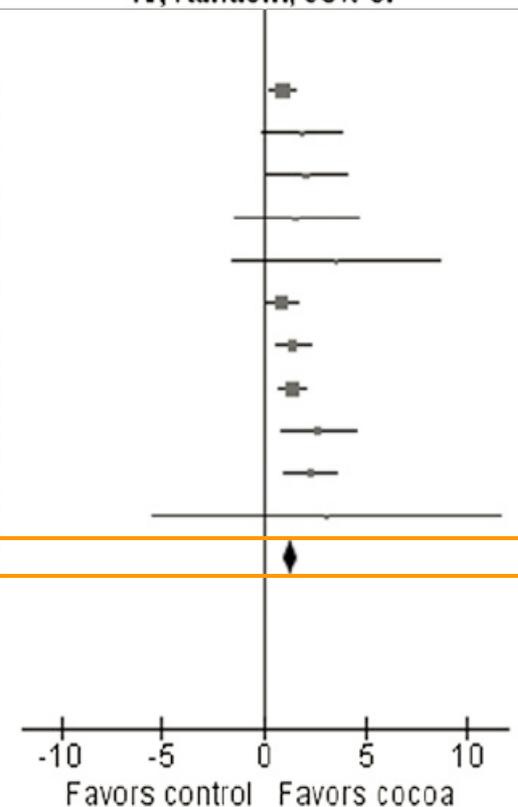


Effect of Cocoa Flavanols on Flow-mediated Dilation

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
2-18 weeks					
Balzer 2008 (38)	0.9	0.357	23.9%	0.90 [0.20, 1.60]	
Davison 2008 (Ex) (41)	1.9	1.026	2.9%	1.90 [-0.11, 3.91]	
Davison 2008 (noEx) (41)	2.1	1.036	2.8%	2.10 [0.07, 4.13]	
Engler 2004 (43)	1.6	1.566	1.2%	1.60 [-1.47, 4.67]	
Farouque 2006 (45)	3.57	2.63	0.4%	3.57 [-1.58, 8.72]	
Grassi 2005 (nBP) (49)	0.9	0.408	18.3%	0.90 [0.10, 1.70]	
Grassi 2005(↑BP) (48)	1.4	0.429	16.6%	1.40 [0.56, 2.24]	
Grassi 2008 (50)	1.4	0.357	23.9%	1.40 [0.70, 2.10]	
Heiss 2010 (54)	2.7	0.94	3.5%	2.70 [0.86, 4.54]	
Njike 2009 (61)	2.3	0.699	6.2%	2.30 [0.93, 3.67]	
Wang-Polagruto 2006 (75)	3.1	4.383	0.2%	3.10 [-5.49, 11.69]	
Subtotal (95% CI)			100.0%	1.34 [1.00, 1.68]	

Heterogeneity: Tau² = 0.00; Chi² = 8.45, df = 10 (P = 0.58); I² = 0%

Test for overall effect: Z = 7.67 (P < 0.00001)



Test for subgroup differences: Chi² = 9.19, df = 1 (P = 0.002), I² = 89.1%

RCT of Cocoa Flavanols (CF) and BP, Glucose Tolerance, and Cognition

- Randomized, double-blind 8 wk trial of high (990 mg/d), medium (520 mg/d), and low (45 mg/d) dose CF.

N=90 (37 M/, 53 F), mean age 69, all with normal cognitive function.

	High (990 mg/d)	Medium (520 mg/d)	Low (45 mg/d)
Systolic BP [†]	↓ ***	↓ ***	↔
Diastolic BP [‡]	↓ ***	↓ ***	↔
Glucose/insulin/HOMA-IR	↓ ***	↓ ***	↔
LDL-Chol/TG	↓ ***	↓ ***	↔
HDL-Chol	↑ **	↑ **	↔
Isoprostanes	↓ **	↓ **	↔
Cognition	+ ¶	+ ¶	↔

[†] ↓ 7-8 mmHg [‡] ↓ 3-5 mmHg

* p <0.05 ** p <0.01 *** p <0.001 ¶ Improved trail making and verbal fluency; MMSE unchanged.

Cocoa Flavanols, Dentate Gyrus Function, and Age-Related Cognition

RCT at Columbia (Brickman, et al. *Nature Neurosci* 2014):

- 37 patients aged 50-69, received either a high (900 mg) or low (10 mg) cocoa flavanol-containing diet for 3 months, double-masked.
 - High flavanol, but not low flavanol, diet enhanced dentate gyrate activity/blood flow, as measured by fMRI.
 - High flavanol diet was associated with significantly better ModBent pattern recognition reaction time scores (marker of age-related memory decline; maps to dentate gyrus function).
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Justification of Amount of Cocoa Tested in COSMOS

- **The 600 mg/day cocoa supplement is a patented cocoa extract containing the compounds associated with its many health benefits, but without the calories, caffeine, fat or dairy, found in chocolate.**
 - **Each 600 mg includes at least:**
 - **80 mg(-) – epicatechins**
 - **50 mg theobromine**
 - **Equivalent content:**
 - **6 tbs of cocoa mix powder**
 - **4 ¾ oz (750 calories) per day of dark chocolate**
 - **2 ½ lbs (5,850 calories) per day of milk chocolate**
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Multivitamins: Background

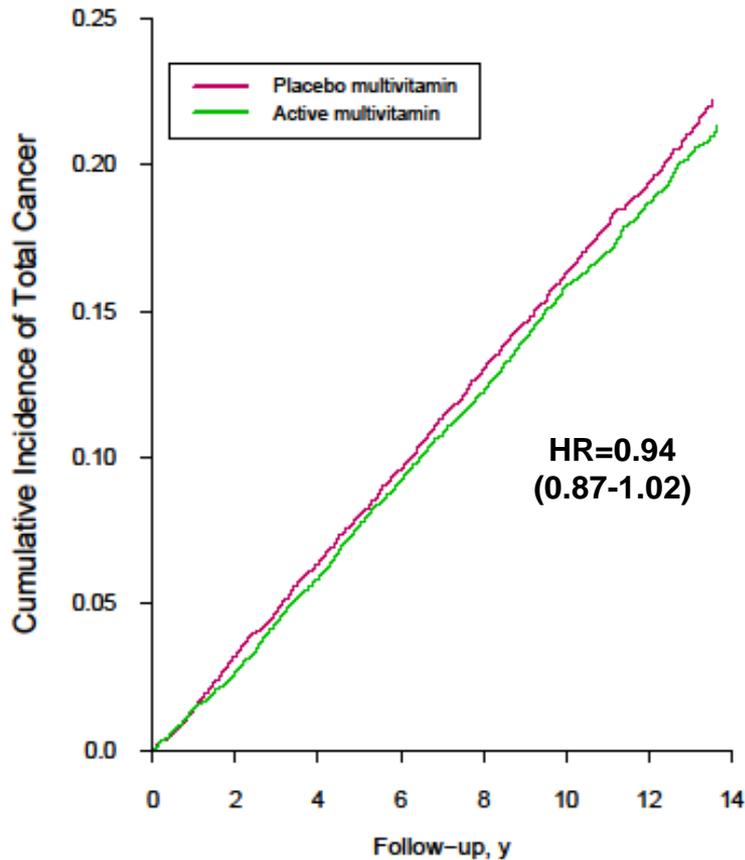
- **More than one-third of adults in the US take multivitamins (MV).**
 - **Basic research suggests how some components of MV might reduce the risk of cancer and CVD. Observational studies have not clearly demonstrated associations of MV with lower risk of either outcome.**
 - **A large-scale randomized trial of a multivitamin in men (the Physicians' Health Study II) suggested benefits for cancer prevention, but no randomized trials have been done in women.**
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Cancer Events by MVM Treatment Assignment

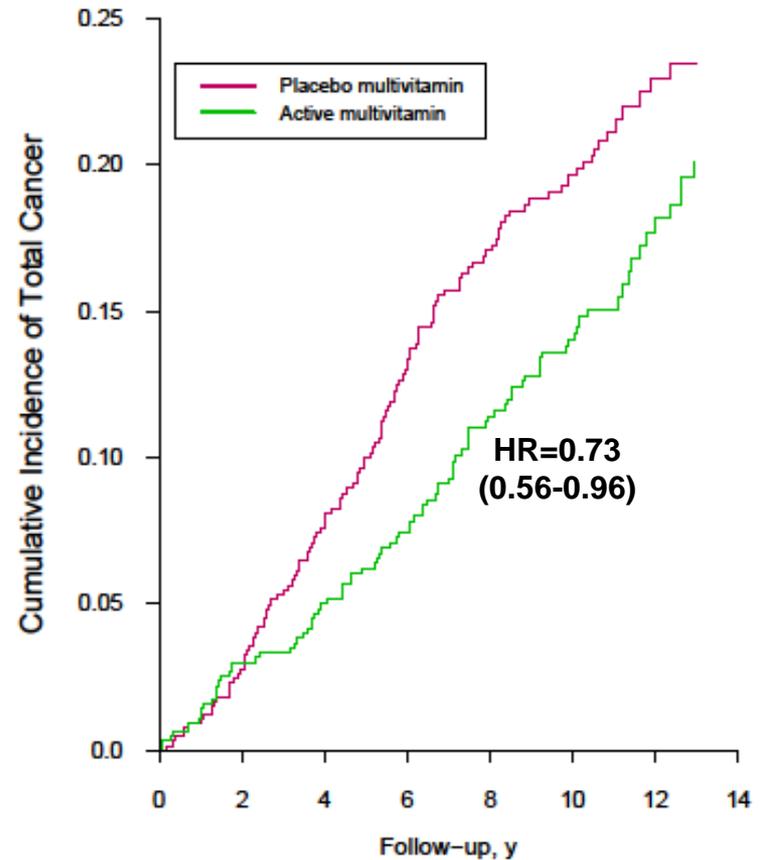
Outcome	Active (n = 7317)	Placebo (n = 7324)	HR (95% CI)	P
Total cancer*	1290	1379	0.92 (0.86-0.998)	.04
Total cancer minus prostate	641	715	0.88 (0.79-0.98)	.02
Prostate cancer	683	690	0.98 (0.88-1.09)	.76
Colorectal cancer	99	111	0.89 (0.68-1.17)	.39
Cancer mortality	403	456	0.88 (0.77-1.01)	.07
Total mortality	1345	1412	0.94 (0.88-1.02)	.13

**For men aged ≥ 70 , HR (95%CI) = 0.82 (0.72-0.93); p for interaction by age = 0.06.*

Primary Prevention



Secondary Prevention



Cardiovascular Events by Multivitamin Treatment Assignment

Outcome	Active (n = 7317)	Placebo (n = 7324)	HR (95% CI)	P
Major cardiovascular events	876	856	1.01 (0.91-1.10)	.91
Total MI	317	335	0.93 (0.80-1.09)	.39
MI death	27	43	0.61 (0.38-0.995)	.048
Total stroke	332	311	1.06 (0.91-1.23)	.48
Cardiovascular death	408	421	0.95 (0.83-1.09)	.47

For men aged ≥ 70 , HR (95% CI) = 0.91 (0.81-1.03); p for interaction by age = 0.04.

Cohort Size/Power

- **N = 18,000 women and men**
(Pilot studies confirm our ability to recruit these numbers.)
 - **Recruitment pool:**
 - N = ~68,000 eligible women from WHI**
 - N = 98,400 men for VITAL respondents**
(**N = ~150,000 VITAL women, if needed**)
 - **With 4 years of treatment, power of 90% to detect RR=0.88 for primary CVD endpoint of MI, stroke, CVD mortality, and coronary revascularization.**
 - **Power = 95% for CVD composite plus all-cause mortality.**
 - **Power is also >90% for RR of 0.84 for total cancer.**
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COSMOS Activities in the Past Year

- **Finalized the study protocol.**
 - **Completed pilot studies to assess recruitment of women and men.**
 - **Developed screening and enrollment questionnaires and FFQ.**
 - **Finalized informed consent forms.**
 - **Collaborated with ancillary study PIs on grant submissions.**
 - **Worked with companies on study pills/placebos/ calendar packaging.**
 - **Planned stability testing of study pills.**
 - **Worked closely with WHI CCC on data management issues.**
 - **Prepared for recruitment mailings (coordinated with WHISH).**
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COSMOS Trial Timeline

- **May 2015**
 - **Response from FDA regarding IND Waiver**
 - **Initial COSMOS enrollment mailings**
 - **August/September 2015**
 - **Start of placebo run-in**
 - **November/December 2015**
 - **Start of randomization into COSMOS**
 - **1 year to enroll and randomize COSMOS trial cohort**
 - **4 years of treatment and follow-up**
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Potential Ancillary Studies

- **Spring 2014:** *The WHI Ancillary Study Committee approved 10 studies for Fall 2014 NIH R01 grant submissions covering diverse topics, including:*
 - **Cognitive Function** (Wake Forest University)
 - **Diabetes** (Brown University and Brigham and Women's Hospital)
 - **Hypertension** (Brigham and Women's Hospital)
 - **Arterial Health** (University of California at San Diego)
 - **Cerebral Blood Flow/MRI** (Brigham and Women's Hospital)
 - **Heart Failure** (Brown University)
 - **Fracture/Bone Health** (Brigham and Women's Hospital)
 - **Sarcopenia/Muscle Function** (The Ohio State University)
 - **Mood/Depression** (Brigham and Women's Hospital)
 - **Cataract/Age-related Macular Degeneration** (Brigham and Women's Hospital)
 - *July 2015 NIH R01 grant resubmissions expected.*
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Opportunities for Additional Ancillary Studies

- *We expect additional ancillary studies for the COSMOS trial to be proposed, submitted, and funded through a variety of potential mechanisms in research areas such as:*
 - **Biomarker studies**
 - **Genetic studies (e.g. telomere length)**
 - **Other imaging studies**
 - **Other vascular outcomes**
 - **Physical performance**
 - **Quality of life**
 - **Site-specific cancers**
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Conclusions

- **Cocoa and multivitamins are promising interventions for reducing risks of CVD and cancer, but conclusive evidence for their efficacy is lacking.**
- **The COSMOS trial will be the first large-scale randomized clinical trial of cocoa in either men or women and the first large-scale trial of multivitamins in women, and will be exceptionally cost-effective.**



Thank you!