Main findings from the COocoa Supplement and Multivitamin Outcomes Study (COSMOS)

Howard D. Sesso, ScD, MPH
Associate Director, Division of Preventive Medicine
Associate Professor of Medicine
Division of Preventive Medicine
Brigham and Women’s Hospital
Harvard Medical School

JoAnn E. Manson, MD, DrPH
Chief, Division of Preventive Medicine
Professor of Medicine
Michael and Lee Bell Professor of Women’s Health
Brigham and Women’s Hospital
Harvard Medical School

Garnet L. Anderson, PhD
Senior Vice President and Director
Public Health Sciences Division, Fred Hutch
Principal Investigator, WHI Clinical Coordinating Center

Disclosures

• **Mars Edge**: Investigator-initiated grants for infrastructure support and donation of COSMOS study pills and packaging

• **Pfizer Consumer Healthcare (now part of GSK Consumer Healthcare)**: Donation of COSMOS study pills and packaging
Background – Cocoa Flavanols

• Cocoa comes from the bean of the cacao tree, *Theobroma cacao*, which when processed forms cocoa and chocolate products.
  ▪ Also contains modest amounts of caffeine and theobromine.
• Cocoa’s potential benefits are likely due to its high flavanol content.
  ▪ Flavanols are also found in tea leaves, berries, grapes, and other foods.
• Observational studies (dietary flavanol intake) have been inconsistent.
• Short-term trials of flavanols (including cocoa and cocoa products) have found potential cardiovascular benefits (including blood pressure lowering, blood vessel dilation, anti-inflammatory effects).
COSMOS is *not* a chocolate trial – sorry!

Chocolate Candy  COSMOS
Background – Multivitamins

• More than one-third of adults in the US take multivitamin-multimineral supplements (MVMs).
• Basic research suggests how some components of MVMs might reduce the risk of cancer and cardiovascular disease (CVD).
• Observational studies have been inconsistent regarding cancer and CVD.
• We previously completed a large-scale randomized trial of a MVM in 14,641 men (Physicians’ Health Study II) over 11 years of follow-up:
  • 8% significant reduction in total cancer.
  • 27% significant reduction in those with a history of cancer.
  • There had been no previous large-scale randomized trials of MVMs in women.
COSMOS Primary Aims

1. To test whether a cocoa extract supplement (with 500 mg/day cocoa flavanols) reduces risk of total CVD events (heart attack, stroke, CVD death, heart artery procedures (e.g., bypass or stent), other artery procedures (e.g., in neck or leg), or unstable angina.

2. To test whether a multivitamin (as Centrum Silver) supplement reduces risk of total invasive cancer.
COSMOS Secondary Aims

1. To test whether the study pills reduce risk of:
   • Combined outcome of total CVD plus death from all causes.
   • Individual types of CVD events or common types of cancers (breast, colorectal, melanoma, and lung).
   • Major CVD events.
   • Death from all causes.

2. To test whether a multivitamin reduces cancer among those with a history of cancer at baseline.
Recruitment

- Recruitment from existing cohorts
  - Women’s Health Initiative (WHI) Extension Study participants
  - VITamin D and OmegA-3 Trial (VITAL) participants contacted but not randomized
- Volunteers via ads and media
- Direct mass mailings
  - >2.6 million invitation letters sent
Follow-up and outcome Assessment

• Compliance with study pills >80% for both interventions

• Median follow-up = 3.6 years

• Participants reporting an outcome were asked to sign a release form for medical record review

• Lost to follow-up = 0.3%
Compliance >80% for both interventions!
COSMOS Baseline Characteristics

Distribution by age and sex

Recruitment Source

- WHI: 32%
- VITAL: 32%
- Other: 22%
- 46%
## COSMOS Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Total (N=21,442)</th>
<th>Cocoa extract (N=10,719)</th>
<th>Placebo (N=10,723)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean</td>
<td>72.1 years</td>
<td>72.1 years</td>
<td>72.1 years</td>
</tr>
<tr>
<td></td>
<td>(Women = 74.2; Men = 69.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>59.1%</td>
<td>59.1%</td>
<td>59.0%</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>2.6%</td>
<td>2.5%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>90.0%</td>
<td>89.8%</td>
<td>90.2%</td>
</tr>
<tr>
<td>African-American</td>
<td>5.3%</td>
<td>5.2%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>2.3%</td>
<td>2.6%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Other</td>
<td>2.4%</td>
<td>2.5%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Education: more than high school</td>
<td>89.2%</td>
<td>89.3%</td>
<td>89.1%</td>
</tr>
<tr>
<td>Never smoker</td>
<td>54.7%</td>
<td>54.6%</td>
<td>54.9%</td>
</tr>
<tr>
<td>Total MET-hours/week from exercise, median</td>
<td>17.1</td>
<td>17.3</td>
<td>17.0</td>
</tr>
<tr>
<td>Chocolate consumption at least weekly</td>
<td>68.2%</td>
<td>68.5%</td>
<td>67.8%</td>
</tr>
<tr>
<td>Multivitamin use before run-in</td>
<td>41.2%</td>
<td>41.6%</td>
<td>40.8%</td>
</tr>
<tr>
<td>History of CVD*</td>
<td>6.0%</td>
<td>5.9%</td>
<td>6.1%</td>
</tr>
<tr>
<td>History of cancer†</td>
<td>16.6%</td>
<td>16.6%</td>
<td>16.6%</td>
</tr>
</tbody>
</table>

* Self-reported coronary revascularization, unstable angina, carotid artery disease, or peripheral artery disease.
† Self-reported and excludes non-melanoma skin cancer.
## Effect of cocoa flavanols on cardiovascular events: Intention-to-treat analyses (once randomized, always analyzed)

<table>
<thead>
<tr>
<th></th>
<th>Cocoa extract (n=10,719)</th>
<th>Placebo (n=10,723)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total CVD</td>
<td>410</td>
<td>456</td>
<td>↓10%</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart attack</td>
<td>88</td>
<td>101</td>
<td>↓13%</td>
</tr>
<tr>
<td>Stroke</td>
<td>113</td>
<td>124</td>
<td>↓9%</td>
</tr>
<tr>
<td><strong>CVD death</strong></td>
<td>76</td>
<td>104</td>
<td>↓27%*</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>166</td>
<td>175</td>
<td>↓5%</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>46</td>
<td>46</td>
<td>0%</td>
</tr>
<tr>
<td>All-cause death</td>
<td>353</td>
<td>397</td>
<td>↓11%</td>
</tr>
<tr>
<td><strong>Other outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major CVD event (heart attack, stroke, CVD death)</td>
<td>255</td>
<td>304</td>
<td>↓16%*</td>
</tr>
</tbody>
</table>

*Statistically significant
Effect of cocoa flavanols on cardiovascular events: Compliance-based analyses (only those taking assigned pills)

<table>
<thead>
<tr>
<th></th>
<th>Cocoa extract (n=10,719)</th>
<th>Placebo (n=10,723)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total CVD</td>
<td>298</td>
<td>349</td>
<td>↓15%*</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart attack</td>
<td>68</td>
<td>81</td>
<td>↓14%</td>
</tr>
<tr>
<td>Stroke</td>
<td>75</td>
<td>97</td>
<td>↓25%</td>
</tr>
<tr>
<td><strong>CVD death</strong></td>
<td>44</td>
<td>69</td>
<td>↓39%*</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>130</td>
<td>146</td>
<td>↓11%</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>32</td>
<td>33</td>
<td>0%</td>
</tr>
<tr>
<td>All-cause death</td>
<td>166</td>
<td>203</td>
<td>↓18%</td>
</tr>
<tr>
<td><strong>Other outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major CVD event (heart attack, stroke, CVD death)</td>
<td>176</td>
<td>228</td>
<td>↓24%*</td>
</tr>
</tbody>
</table>

* Statistically significant
Other results for cocoa flavanols

• No statistically significant effect of cocoa flavanols on:
  ▪ Total invasive cancer
  ▪ Breast cancer
  ▪ Colorectal cancer
  ▪ Lung cancer
  ▪ Cancer mortality

• No side effects for cocoa flavanols versus placebo except:
  ▪ Small significant increased risk of stomach upset or pain or nausea, which was short-term.
  ▪ Significant reductions in flu-like symptoms, migraine, and other headaches.

Sesso HD, Manson JE, Aragaki AK et al. AJCN 2022
Conclusions

• Those randomized to cocoa extract had a 10% lower rate of total CVD over 3.6 years than those assigned to placebo, but this was not statistically significant.
  ▪ 27% reduction in CVD death.
  ▪ No significant effect on other individual cardiovascular endpoints.
  ▪ 16% reduction in a more limited composite outcome of major cardiovascular events.
  ▪ No effect on total and major site-specific invasive cancers.

• The overall results for cocoa extract were promising, but not definitive, for CVD prevention.

• Cocoa flavanol supplementation was safe.

• More analyses will elucidate the role of cocoa flavanols in CVD prevention and other aging-related outcomes (e.g. clinic assessments, biospecimens).
## Effect of a multivitamin on invasive cancer: Intention-to-treat analyses (once randomized, always analyzed)

<table>
<thead>
<tr>
<th></th>
<th>Multivitamin (n=10,720)</th>
<th>Placebo (n=10,722)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total invasive cancer</td>
<td>518</td>
<td>535</td>
<td>↓3%</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>93</td>
<td>87</td>
<td>↑6%</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>38</td>
<td>29</td>
<td>↑30%</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>41</td>
<td>66</td>
<td>↓38%*</td>
</tr>
<tr>
<td>All-cause death</td>
<td>362</td>
<td>388</td>
<td>↓7%</td>
</tr>
<tr>
<td>Other outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>93</td>
<td>113</td>
<td>↓18%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>34</td>
<td>40</td>
<td>↓14%</td>
</tr>
<tr>
<td>Cancer mortality</td>
<td>116</td>
<td>109</td>
<td>↑6%</td>
</tr>
</tbody>
</table>

*S Sesso HD, Rist PM, Aragaki AK et al. AJCN 2022*

* Statistically significant
Effect of a multivitamin on total invasive cancer by subgroups

• There was no modifying effect of the following with the multivitamin intervention on total invasive cancer:

  ▪ Sex
  ▪ Age
  ▪ Prior history of cancer
  ▪ Smoking status
  ▪ Number of cardiovascular risk factors
  ▪ Statin use
  ▪ Aspirin use
  ▪ Multivitamin use before the run-in
  ▪ Prior use of dietary supplements
  ▪ Fruit and vegetable intake
  ▪ Randomized cocoa extract use
Other results for multivitamins

• No statistically significant effect of a multivitamin on:
  ▪ Total CVD
  ▪ Individual cardiovascular endpoints
  ▪ CVD death
  ▪ Major CVD event (heart attack, stroke, or CVD death)

• No side effects for a multivitamin versus placebo except:
  ▪ Modest significant increased risk of gastrointestinal bleeding.
  ▪ Small significant reduction in easy bruising.
  ▪ Significant reductions in stomach upset or pain, diarrhea, and skin rash.

Sesso HD, Manson JE, Aragaki AK et al. AJCN 2022
Effect of a multivitamin on nutritional biomarkers

• We measured vitamin D, vitamin B$_{12}$, and folate in 399 COSMOS participants with baseline and ≥1 follow-up blood sample.
Conclusions

• Taking a multivitamin for 3.6 years did not reduce total invasive cancer.
  ▪ No effect on major site-specific cancers
  ▪ Exception: 38% reduction in lung cancer.
  ▪ No effect on total CVD, CVD death, or all-cause mortality.
  ▪ No effect on cancer among those with an initial history of cancer (in contrast to PHS II).

• Multivitamin use was safe.

• Multivitamin use increased levels of nutritional biomarkers.

• Future studies should clarify the role of multivitamin use on nutritional status and its effects on cancer, CVD, and other aging-related outcomes.
Potential limitations

• Cocoa flavanols and CVD
  ▪ **Total CVD outcome was too broad**: A narrower but more clinically relevant (unspecified) major CVD outcome was statistically significant.
  ▪ **Multiple testing**: Not every result can be expected to be statistically significant, yet the overall pattern of results are highly suggestive of cardiovascular benefits.

• Multivitamins and cancer
  ▪ **COSMOS too short**: Cancer can take time to develop and it is difficult to detect a small-to-moderate effect on cancer.
  ▪ **Extension to other multivitamins**: Unclear whether the COSMOS results apply to just the Centrum Silver multivitamin formulation, or to all multivitamins.
  ▪ **Role of baseline nutritional status**: We need to better understand how your current diet may impact the effects of a multivitamin on health outcomes.
Acknowledgements

• All 21,442 COSMOS participants, including 4,611 WHI participants
• Brigham and Women’s Hospital [BWH]
• Fred Hutchinson Cancer Research Center [FHCRC]
• Women’s Health Initiative [WHI]
• Data Safety and Monitoring Board [DSMB]
• Mars Edge
• Pfizer Consumer Healthcare [now GSK Consumer Healthcare]
• Contract Pharmacal Corp
Division of
Preventive Medicine

Department of Medicine

https://prevmed.bwh.harvard.edu/

Thank you!

Howard D. Sesso, ScD, MPH and JoAnn E. Manson, MD, DrPH
hsesso@bwh.harvard.edu and jmanson@rics.bwh.harvard.edu