



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

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Cocoa flavanol paper: *H. Sesso,\* J. Manson,\* A. Aragaki, P. Rist, L. Johnson, G. Friedenber, T. Copeland, A. Clar, S. Mora, M.V. Moorthy, A. Sarkissian, W. Carrick, G. Anderson*

Multivitamin paper: *H. Sesso,\* P. Rist,\* A. Aragaki, S. Rautiainen, L. Johnson, G. Friedenber, T. Copeland, A. Clar, S. Mora, M.V. Moorthy, A. Sarkissian, J. Wactawski-Wende, L. Tinker, W. Carrick, G. Anderson, J. Manson*

# 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

**Join the COcoa Supplement and Multivitamin Outcomes Study (COSMOS)**

**Cocoa extract** may reduce the risk of heart disease and stroke in older adults. **Multivitamins** may help reduce the risk of cancer. Researchers at Brigham and Women's Hospital, a teaching affiliate of Harvard Medical School, Fred Hutchinson Cancer Research Center, and colleagues will examine the benefits and risks of these nutritional supplements in an exciting new study conducted by mail.

COSMOS, a landmark clinical trial of 18,000 people throughout the U.S., will test whether taking **two cocoa extract capsules** and a standard **multivitamin tablet** every day can reduce the risk of developing cardiovascular disease and cancer.

**Who is eligible to participate?**  
Women 65 and older and men 60 and older in the U.S. are eligible to participate. Participants should be willing to forego personal use of multivitamin supplements to be eligible.

**Who is not eligible to participate?**  
Anyone who has ever had a heart attack or stroke, a new diagnosis of cancer within the past 2 years, or a major illness that would prevent them from participating in a 4-year study.

For more information, visit [www.cosmostrial.org/parade](http://www.cosmostrial.org/parade), or call 800-633-6913





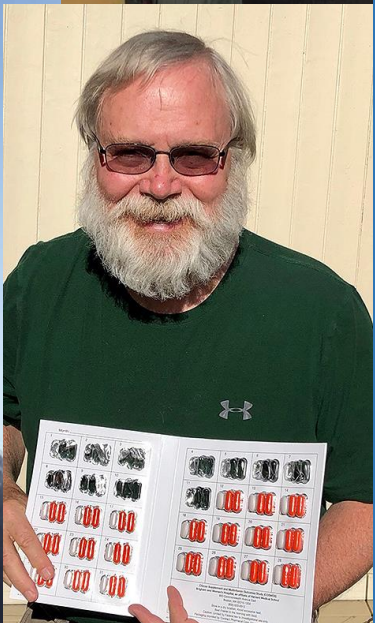
# Follow-up and outcome Assessment

- 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%



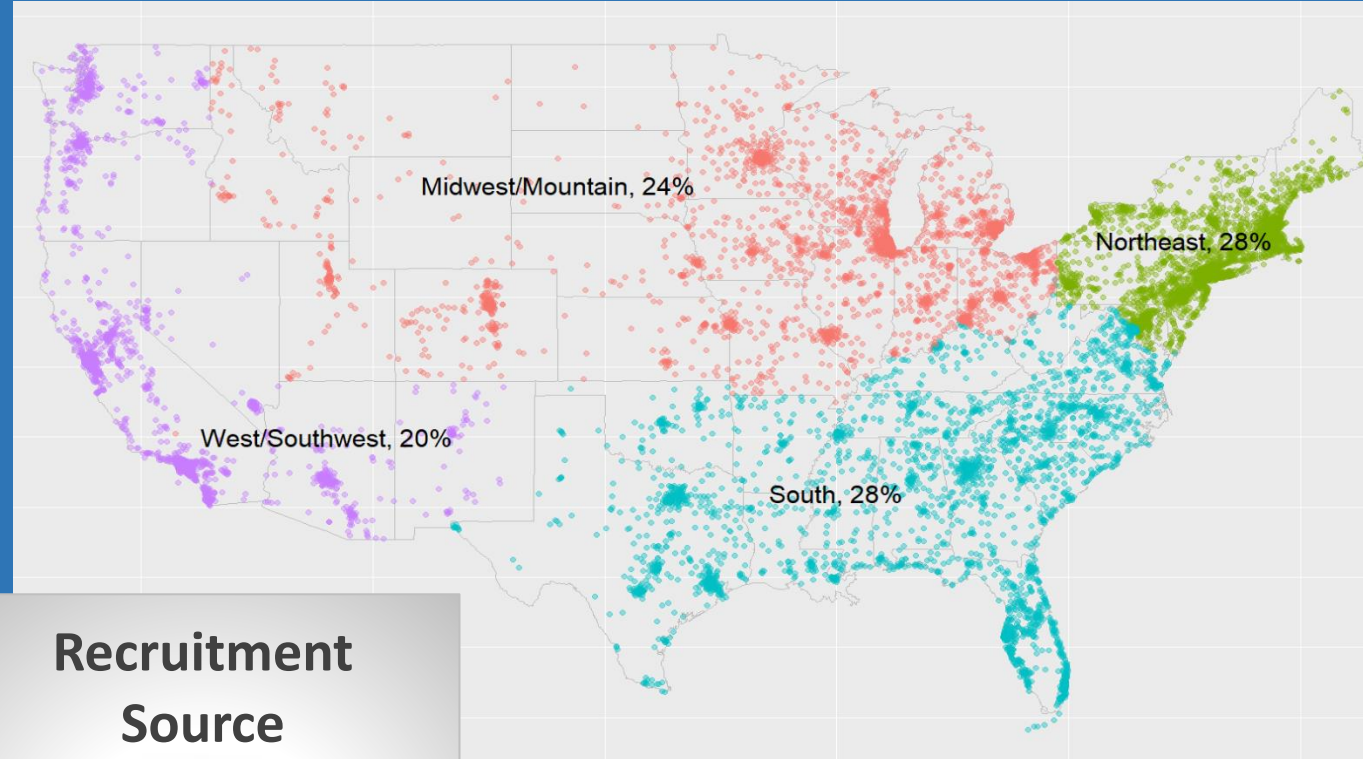
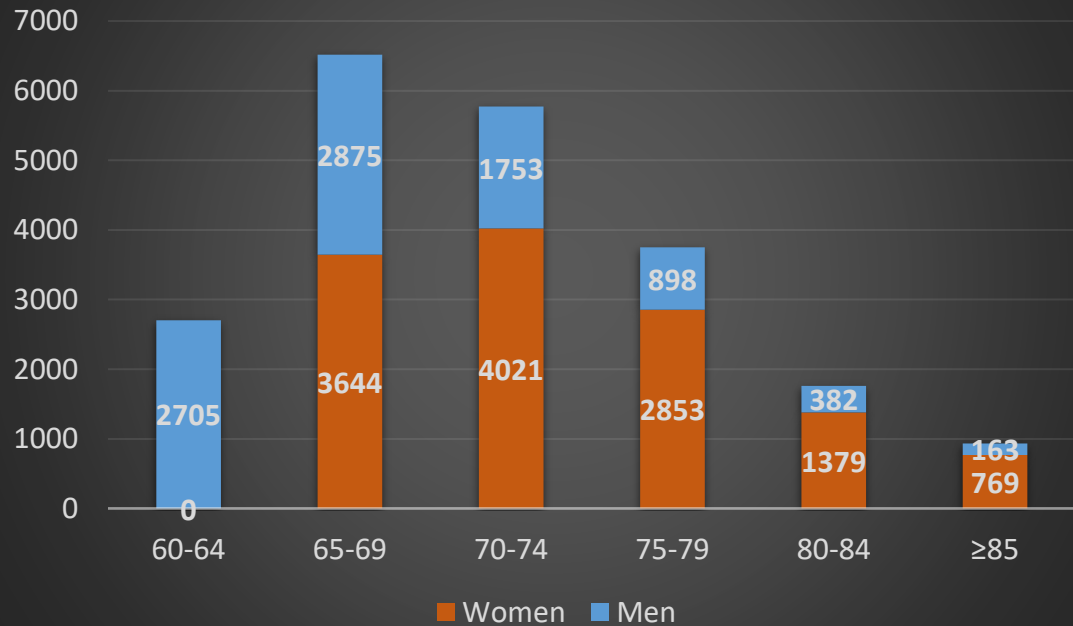


Compliance >80% for both interventions!

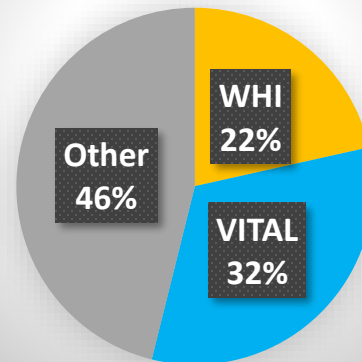


# COSMOS Baseline Characteristics

## Distribution by age and sex



## Recruitment Source



# COSMOS Baseline Characteristics

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

\* 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)

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

\* Statistically significant



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

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

\* 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.

# 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)

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

\* Statistically significant



# Effect of a multivitamin on total invasive cancer by subgroups

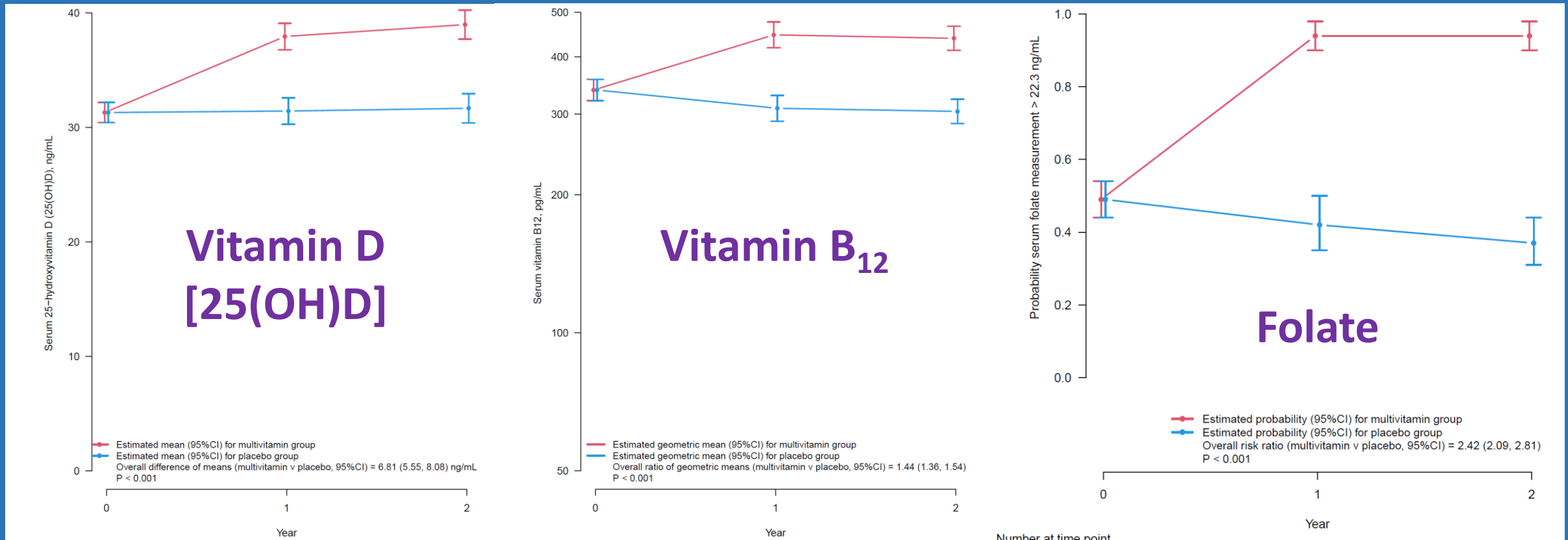
- There was no modifying effect of the following with the multivitamin intervention on total invasive cancer:
  - Sex
  - Age
  - **Prior history of cancer**
  - Smoking status
  - Number of cardiovascular risk factors
  - Statin use
  - Aspirin use
  - Multivitamin use before the run-in
  - Prior use 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.

# Effect of a multivitamin on nutritional biomarkers

- We measured vitamin D, vitamin B<sub>12</sub>, 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 takes 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



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# Thank you!

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