



**The *CO*coa Supplement and *Multivitamin Outcomes Study (COSMOS)*:  
A Randomized Trial of Cocoa Flavanols and Multivitamins  
in the Prevention of CVD and Cancer**

---

**JoAnn E. Manson, MD, DrPH**

**Howard D. Sesso, ScD, MPH**

**Brigham and Women's Hospital**

**Harvard Medical School**

**Garnet L. Anderson, PhD**

**Fred Hutchinson Cancer Research Center**

***WHI Investigators Meeting***

***May 5, 2016***

# **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.**
-

# **COSMOS Is Not a Chocolate Study (Sorry!)**



**Chocolate Candy**



**COSMOS**

# Comparison of Chocolate and Cocoa Flavanols

To get 750 mg of flavanols from chocolate, it takes *about*\*

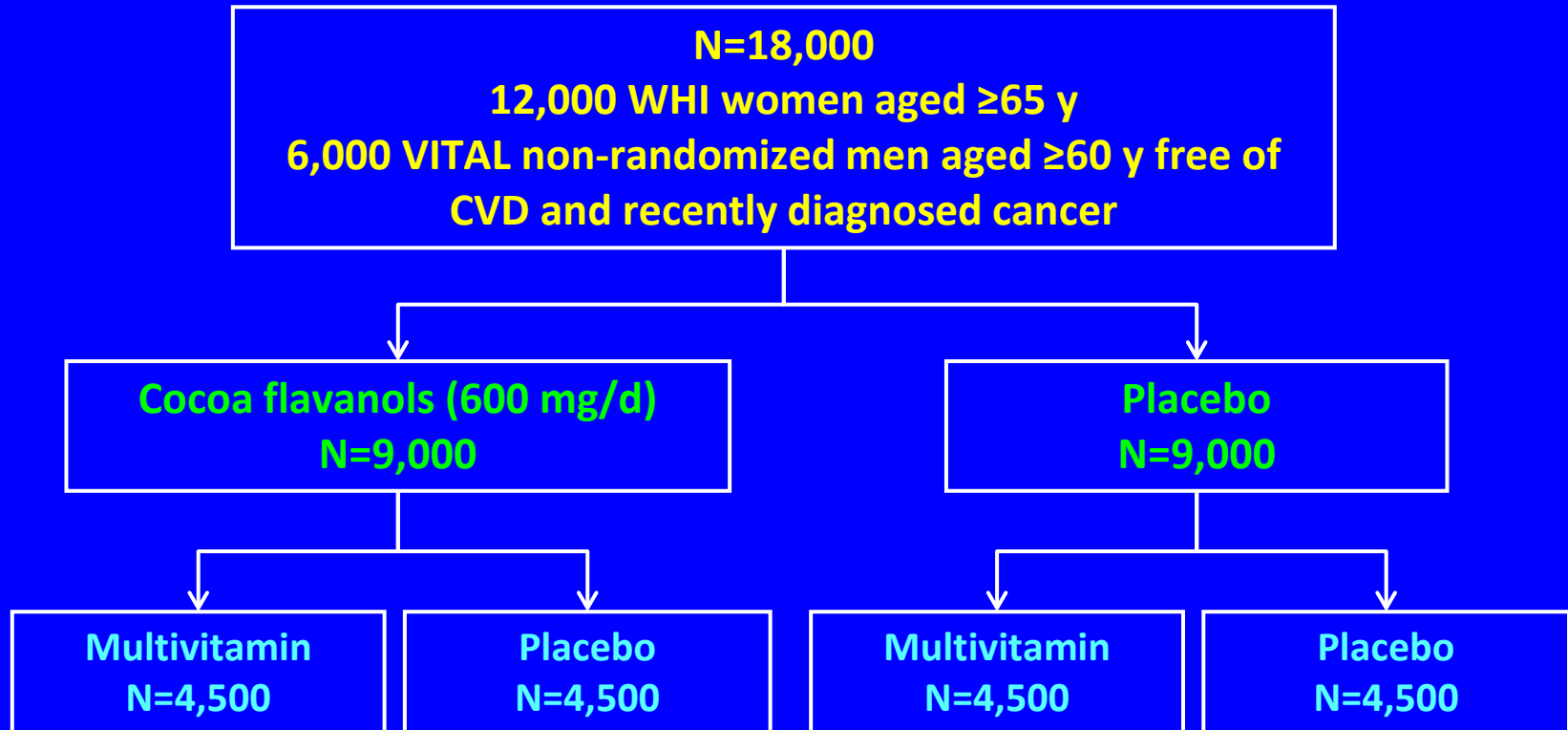


<b>Cocoa Powder</b> 6 Tbs. 70 cals	<b>Baking</b> 1½ oz. 270 cals	<b>Semi-sweet Chips</b> 5½ oz. 740 cals	<b>Dark</b> 4¾ oz. 750 cals	<b>Syrup</b> 3¾ cups 3,170 cals	<b>Milk</b> 2½ lb. 5,850 cals
--	-------------------------------------	---	-----------------------------------	---------------------------------------	-------------------------------------

\*All numbers are averages.



# COcoa Supplement and Multivitamin Outcomes Study (COSMOS)



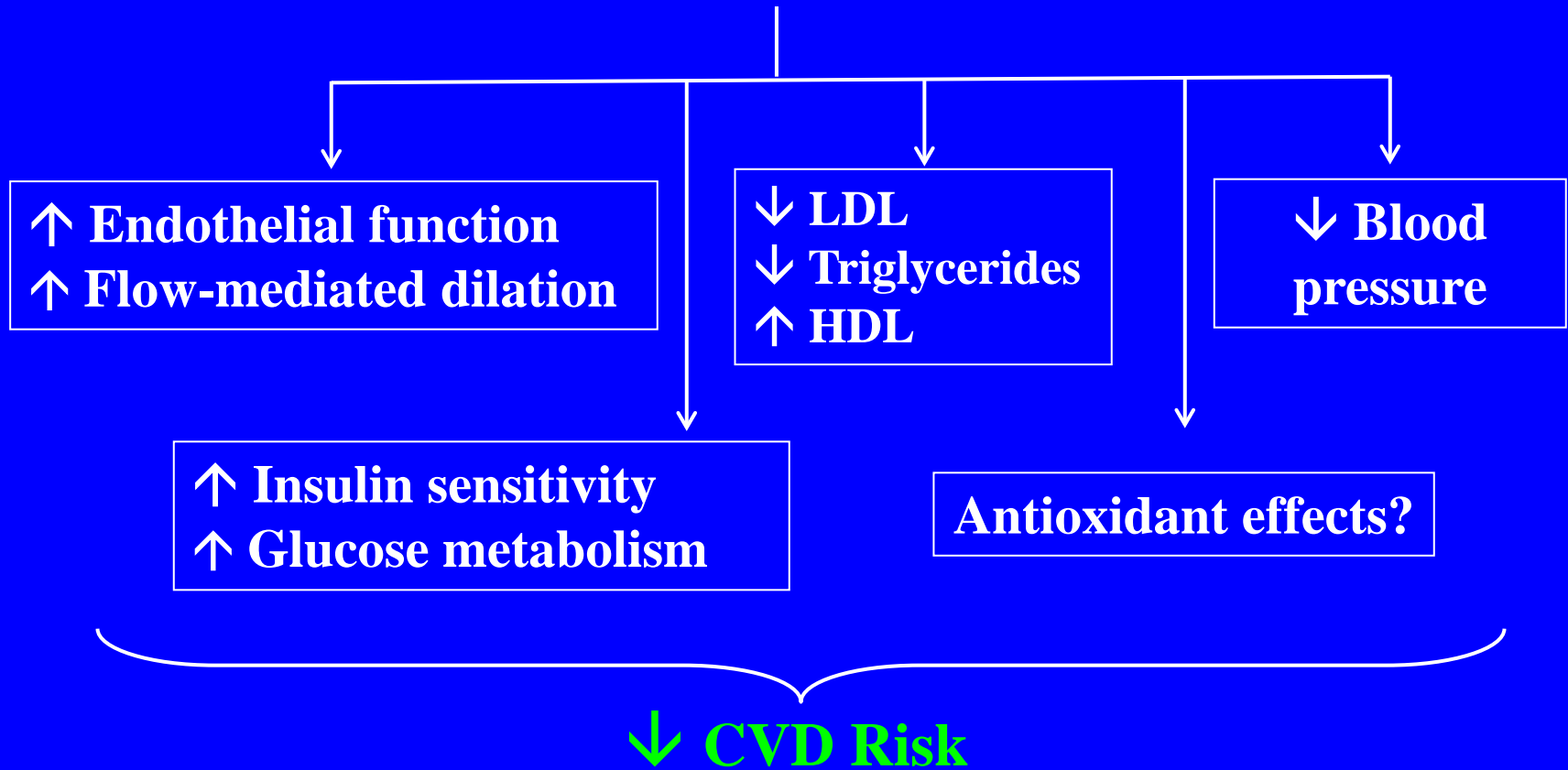
**Mean Treatment Period** = 4.0 years.

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

**Baseline Blood/Urine Collection:** ~6000 participants; F/U samples in a subgroup.

# Multiple Mechanisms Through Which Cocoa Products May Lower the Risk of CVD

## Cocoa Products



# 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.**
-

# 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  $\geq 70$ , HR (95%CI) = 0.82 (0.72-0.93); p for interaction by age = 0.06.*



# Cohort Size/Power

---

- **N = 18,000 women and men**  
**Recruitment pool:**
    - N = ~71,000 eligible women from WHI**
    - N = 98,400 men for VITAL respondents**  
**(N = ~140,000 VITAL women, if needed)**
  - **With 4 years of treatment, power of 90% to detect RR=0.88 for primary CVD endpoint.**
  - **Power = 95% for CVD composite plus all-cause mortality.**
  - **Power is also >90% for RR of 0.84 for total cancer.**
-

## **COSMOS Activities in the Past Year**

---

- **Finalized the study protocol, consent forms, and questionnaires.**
  - **Worked with companies on study pills/placebos/ calendar packaging, and stability testing of study pills.**
  - **Worked closely with WHI CCC on data management issues.**
  - **Collaborated with ancillary study PIs on grant submissions.**
  - **Recruitment mailings (ongoing).**
  - **Began placebo run-in phase in December 2015 (now >9000).**
  - **Began randomizations in April 2016.**
-

# COSMOS Trial Timeline

---

- **June 2015**
    - Initial COSMOS enrollment mailings.
  - **December 2015**
    - Start of 3-6 month placebo run-in.
  - **April 2016**
    - Start of randomization into COSMOS.
  - **Early 2017**
    - Completion of COSMOS enrollment and randomization.
  - **Fall 2020**
    - Potential end of planned trial based on a median of 4 years of treatment and follow-up.
-

## **COSMOS Recruitment: WHI Extension Study**

---

*Current projections for the number of WHI participants expected to be randomized into COSMOS range **between 6,000 and 7,000** women. While response and eligibility rates among the WHI women have been remarkably high, the projected numbers are below our target of 12,000 women randomized into COSMOS and we will need to add both women and men from VITAL respondents.*

---

# COSMOS Ancillary Studies

---

- **Spring 2014:** *The WHI Ancillary Study Committee approved several studies for NIH R01 grant submissions:*
  - **July 2015 onward:** *NIH R01 grant re-submissions*
    - **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** (BWH)
  - **Fall 2015:** **Cognition / ModBent** (Columbia University)
-

# COSMOS Biospecimen Subcohort

---

- Supported through Mars Symbioscience and pending NIH grants.
  - Baseline blood collection (n=6000)
  - Repeat blood collections
    - 500 @Year 1
    - 1000 @Year 2
    - 1000 @Year 4
  - Home- or clinic-based visit through EMSI
    - Fasting blood and urine collection
    - Seated BP
    - Height, weight, waist and hip circumference
  - Participants can also choose to collect blood/urine (only) on their own.
  - Ideal opportunity for studies of biomarkers and genetic factors.
-

# COSMOS Clinical Subcohort

---

- **500 women and men**
  - **1 clinical site at BWH, Boston, MA**
  - **Baseline and 2-year clinical visits**
    - **Fasting blood and spot urine collection**
    - **Seated and 24-hour ambulatory BP**
    - **Cognitive function**
      - **ModBent**
      - **NIH Toolbox**
      - **Other cognitive assessments**
    - **Physical function**
    - **Anthropometric measurements**
      - **Height, weight, waist and hip circumference**
-

# 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. GWAS, telomere length, DNA methylation, etc.)**
    - **Other imaging studies**
    - **Other ancillary outcomes**
-



# 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 RCT of cocoa in either men or women and the first large-scale trial of multivitamins in women.
- Recruitment for the trial is ongoing.



[www.cosmostrial.org](http://www.cosmostrial.org)

*Thank you!*

# COSMOS Research Team

---

- **JoAnn Manson and Howie Sesso**
- **Lu Wang**
- **Nancy Cook**
- **Trisha Copeland, Georgina Friedenber, Jasmah Hanna**
- **Ara Sarkissian**
- **Corey Theodore, Leah Arsenault**
- **BWH Clinic Staff**
- **Kenny Breen**
- **Henry Ouellette and the warehouse staff**
- **Shamikhah Curry and the keypunchers**
- **Kathy Bush, Aruna Pradhan and the blood laboratory**
- ***Key Collaborators***
  - **Mars Symbioscience**
  - **Pfizer, Inc. and Contract Pharmacal Corp (CPC)**
  - **Fred Hutchinson Cancer Research Center (WHI)**
  - **WHI Regional Centers**
  - **Columbia University**
  - **Wake Forest University**
  - **Examination Management Services, Inc. (EMSI)**