

# **A Randomized Trial of a Multivitamin (MVM) in the Prevention of Cardiovascular Disease in Men: The Physicians' Health Study (PHS) II**

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## **Presenter Disclosure Information**

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

**Relevant Disclosures: Research support: NIH (NCI, NHLBI, NIA, and NEI) and investigator-initiated grant from BASF Corporation. Pills and/or packaging were provided by BASF, Pfizer and DSM Nutrition Products.**

# **A Randomized Trial of a Multivitamin in the Prevention of Cardiovascular Disease in Men: The Physicians' Health Study II**

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**Sesso, Christen, Bubes, Smith, MacFadyen,  
Schvartz, Manson, Glynn, Buring, and Gaziano**

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# Background

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- **More than half of US adults take vitamin supplements and common multivitamins (MVM) are the most widely used.**
- **Basic research suggests how some components of MVM might reduce the risk of cardiovascular disease (CVD). Observational studies have not clearly demonstrated associations of MVM with lower risk of CVD.**
- **There are no large-scale, long-term randomized trials of MVM in the prevention of chronic diseases.**

# Physicians' Health Study (PHS)

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**1982 – 1996:** PHS I enrolled 22,071 male physicians in a trial by mail of aspirin and beta-carotene in the prevention of CVD and cancer.

**1997 – present:** PHS II enrolled 7,641 PHS I participants and 7,000 new physicians in a new trial.

# Physicians' Health Study II: Design

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- Randomized, double-blind, placebo-controlled, factorial design trial conducted by mail among 14,641 male physicians aged 50 and older.
- Evaluated the long-term risks and benefits of
  - vitamin E** (400 IU every other day)
  - vitamin C** (500 mg daily)
  - multivitamin** (daily)
- Primary outcomes: CVD and cancer
- Secondary outcomes: Eye disease and cognitive function

# PHYSICIANS' HEALTH STUDY II RANDOMIZATION SCHEME

Phase I: Mailed Invitations to  
18,763 PHS I participants

Phase II: Mailed invitations  
to 254,597 MDs

11,128  
Enrolled  
in a  
Run-in

7,641

7,000

Randomized  
14,641

Active Vitamin E

Vitamin E Placebo

Active Vitamin C

Vitamin C Placebo

Active Vitamin C

Vitamin C Placebo

Active  
Multi-  
Vitamin

Multi-  
Vitamin  
Placebo

Active  
Multi-  
Vitamin

Multi-  
Vitamin  
Placebo

Active  
Multi-  
Vitamin
































Multi-  
Vitamin  
Placebo

Active  
Multi-  
Vitamin

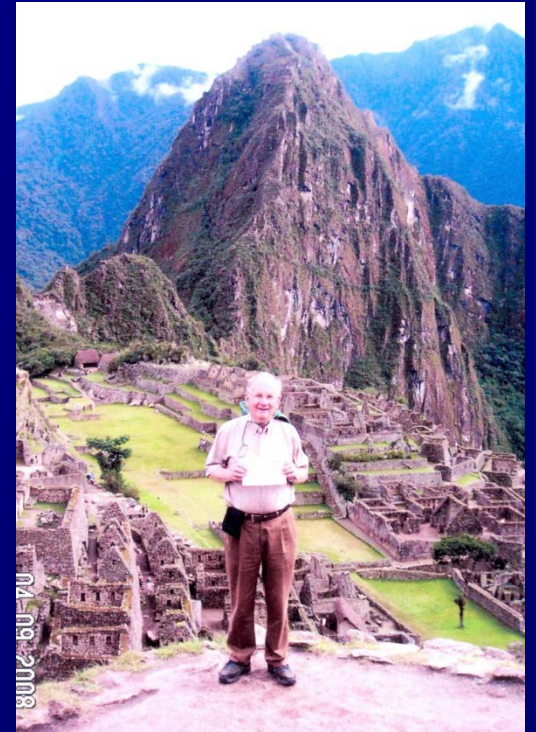
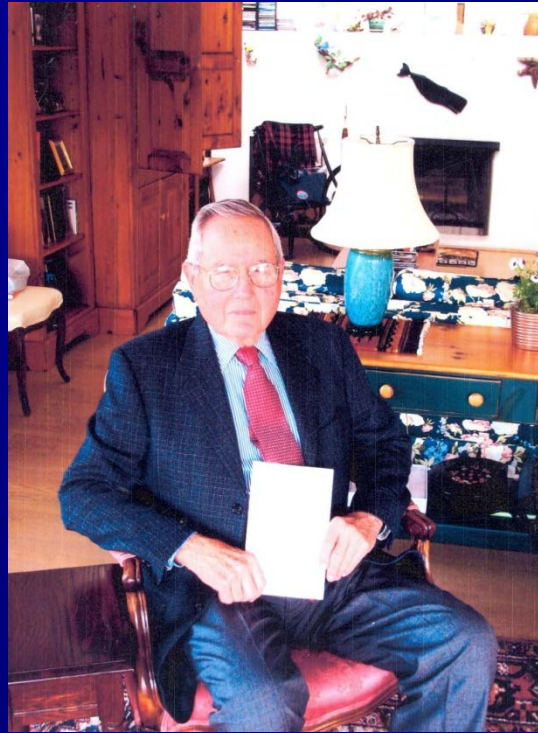
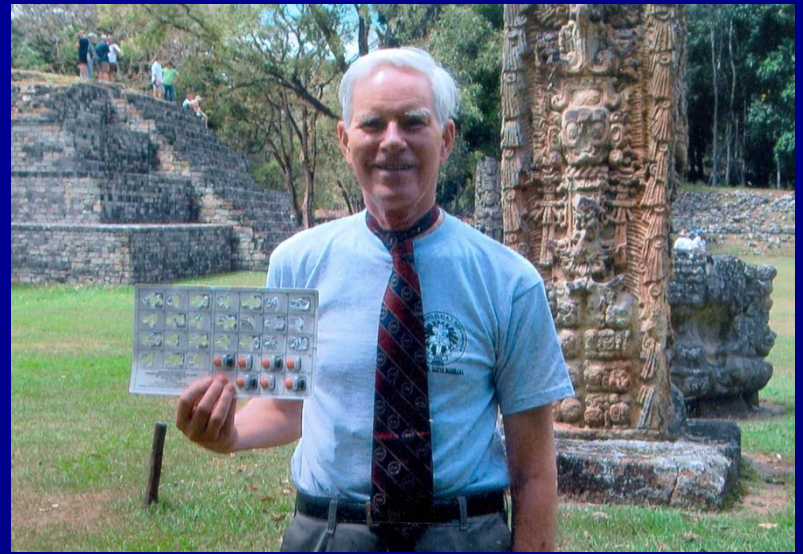
Multi-  
Vitamin  
Placebo



# Monthly Calendar Pack

1 	2 	3 	4 	5 	6 	7 	8 	9 
10 	11 	12 	13 	14 	15 	16 	17 	18 
19 	20 	21 	22 	23 	24 	25 	26 	27 
<p>PHYSICIANS' HEALTH STUDY II BRIGHAM AND WOMEN'S HOSPITAL/HARVARD MEDICAL SCHOOL 900 COMMONWEALTH AVENUE EAST BOSTON, MA 02215-1204 (800) 633-6907 Store in dry location. Avoid excessive heat. Caution: Limited by Federal law to investigational use only <b>WARNING:</b> Package not child-resistant. Keep out of reach of children.</p>					28 	29 	30 	31 







# PHS II: Follow-up

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Mean follow-up was 11.2 years, for a total of more than 164,000 person-years of follow-up.

**MVM compliance:** 77% at 4 years, 72% at 8 years, and 67% at study end.

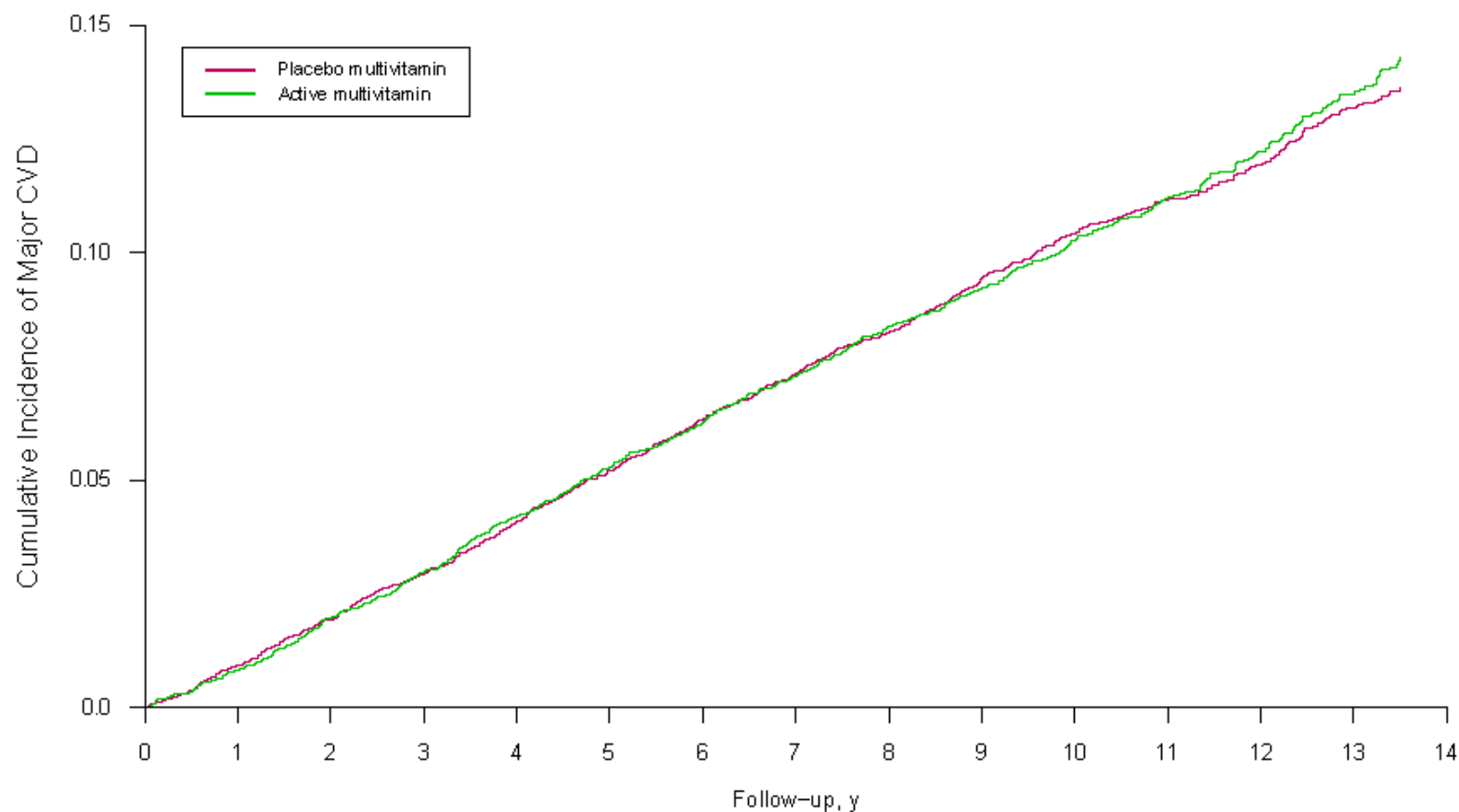
**Primary CVD Outcome:** Major cardiovascular events (nonfatal myocardial infarction (MI), nonfatal stroke, and CVD death)

**Other CVD Outcomes:** Total MI, total stroke, ischemic and hemorrhagic stroke, CVD mortality, and total mortality.

# PHS II: Baseline Characteristics

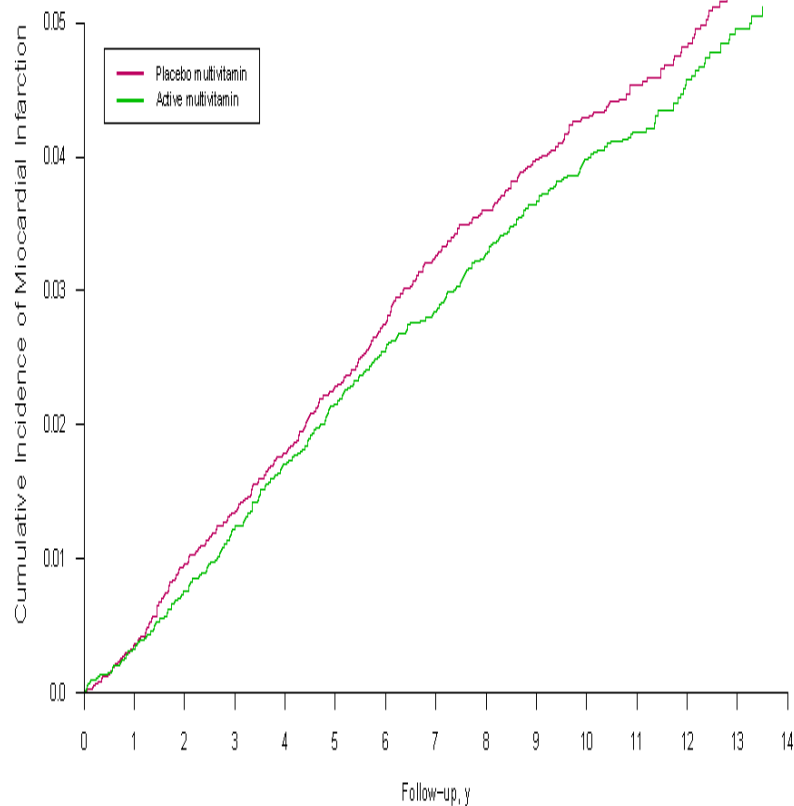
	<u>MVM assignment</u>	
	Active (n = 7317)	Placebo (n = 7324)
Age, mean (SD)	64.2 (9.1)	64.3 (9.2)
BMI, mean (SD)	25.9 (3.4)	26.0 (3.4)
Current smoker, %	3.5	3.7
Exercise $\geq 1$ time/wk, %	62.2	60.7
Current aspirin use, %	77.5	77.3
Hypertension, %	41.8	42.7
Hypercholesterolemia, %	36.0	37.3
Plasma TC, mean (SD)	203.5 (35.5)	203.7 (36.0)
Fruits & vegetables, servings/d	4.26 (2.95-5.75)	4.19 (2.94-5.77)
Whole grains, servings/d	1.13 (0.49-2.00)	1.07 (0.49-1.99)

## Major Cardiovascular Events



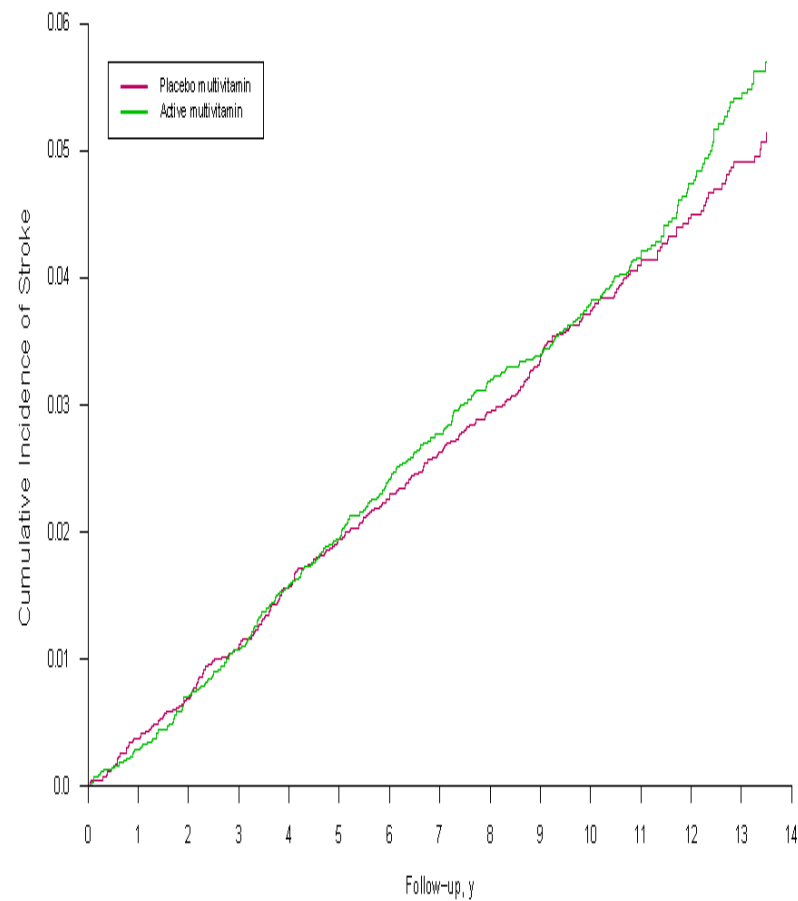
	Number at Risk													
Placebo	7324	7230	7114	6985	6855	6709	6563	6412	6262	6101	5938	3953	2766	2452
Active	7317	7227	7112	7000	6861	6712	6589	6434	6295	6155	5996	3998	2783	2465

## Total Myocardial Infarction



	Number at Risk													
Placebo	7324	7252	7151	7040	6932	6798	6666	6525	6376	6228	6069	4053	2853	2529
Active	7317	7245	7156	7062	6948	6813	6710	6567	6427	6285	6130	4103	2868	2547

## Total Stroke



	Number at Risk													
Placebo	7324	7251	7171	7059	6952	6831	6711	6574	6434	6283	6124	4036	2872	2553
Active	7317	7249	7158	7073	6965	6842	6738	6595	6474	6344	6196	4142	2899	2570



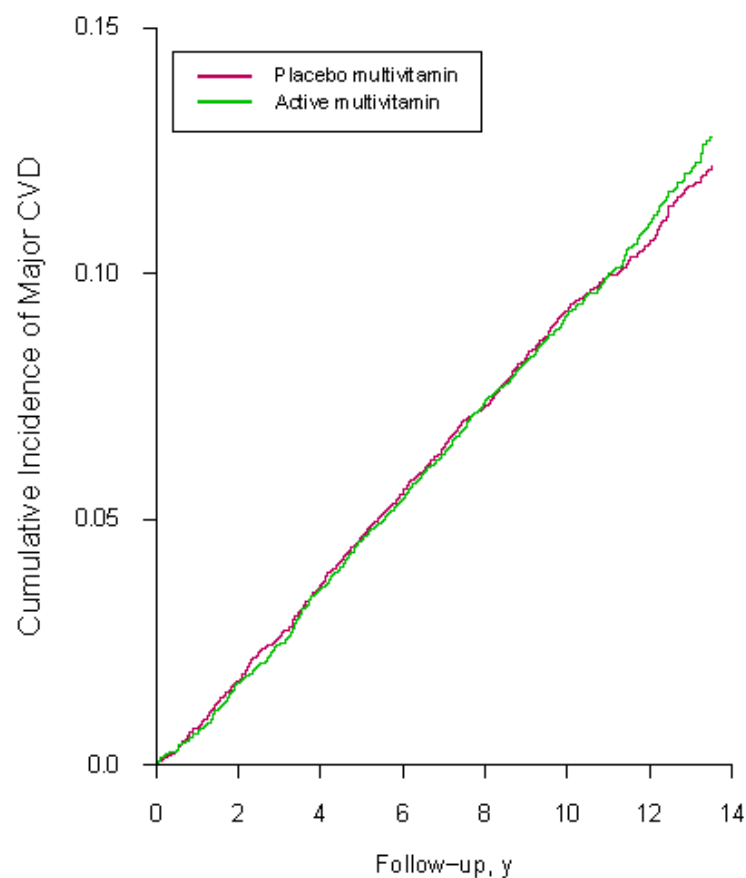
# Cardiovascular Events

## by MVM Treatment Assignment

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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
Stroke death	89	76	1.16 (0.85-1.58)	.34
Ischemic stroke	277	250	1.10 (0.92-1.30)	.29
Hemorrhagic stroke	49	45	1.08 (0.72-1.63)	.69
Cardiovascular death	408	421	0.95 (0.83-1.09)	.47
Total mortality	1345	1412	0.94 (0.88-1.02)	.13

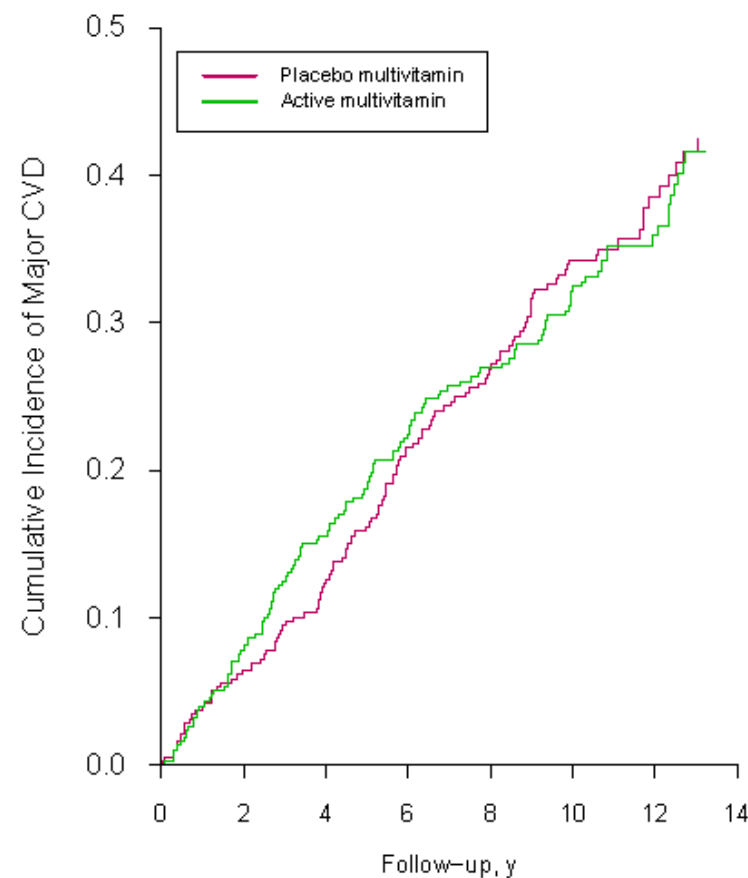
## Primary Prevention



Number at Risk

Placebo	6946	6772	6554	6304	6033	5738	2682
Active	6941	6775	6562	6325	6055	5793	2689

## Secondary Prevention



Number at Risk

Placebo	378	342	301	259	229	200	84
Active	376	337	299	264	240	203	94

# **Possible effect modification Table or Figure**

**(no meaningful effect modification  
noted by baseline risk factors,  
history of CVD, dietary factors, or  
other PHS II randomized treatments)**

# Cancer Events

## by MVM Treatment Assignment

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Outcome	Active (n = 7317)	Placebo (n = 7324)	HR (95% CI)	P
Total cancer	1290	1379	0.92 (0.86-0.998)	.04
Total epithelial cell cancer	1158	1244	0.92 (0.85-0.997)	.04
Total cancer minus prostate	641	715	0.88 (0.79-0.98)	.02
Cancer mortality	403	456	0.88 (0.77-1.01)	.07
Total mortality	1345	1412	0.94 (0.88-1.02)	.13
By baseline history of cancer				
Yes (n=1312)	95	126	0.73 (0.56-0.96)	.02
No (n=13329)	1195	1253	0.94 (0.87-1.02)	.15



# Conclusions

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- **PHS II is the only large-scale randomized trial testing long-term MVM use, finding no effect on major cardiovascular events in men.**
- **The main reason to take a daily MVM remains to prevent vitamin and mineral deficiency.**
- **The decision to take a MVM should consider its beneficial effects on cancer and other important outcomes to be studied.**
- **Additional analyses are planned on relevant CVD outcomes with the hope of extending follow-up of the PHS II cohort.**

# **JAMA Slide**

**(front page of article for  
simultaneous publication)**