Cognition & mental wellbeing: From adulthood to old age
A role for large-scale clinical trials of nutritional supplements

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Conflicts

The opinions shared and expressed in this presentation and webinar are my own and do not reflect the views and opinions of BASF.

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Division of Preventive Medicine, Department of Medicine
Brigham and Women's Hospital & Harvard Medical School

- >20 faculty members with diverse expertise
  - **Epidemiology**
  - Biostatistics
  - Cardiology
  - **Neurology**
  - Endocrinology
  - Oncology
  - **Nutrition**
  - Genetics
  - **Gerontology**

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- *Large-scale randomized clinical trials and epidemiologic studies*
- 5,000 ft^2 blood processing laboratory, and staff
- 6,000 ft^2 blood repository with dozens of high-volume freezers
  - Stored blood and DNA from ~250,000 participants (>2.0M aliquots)

From dietary factor to supplement

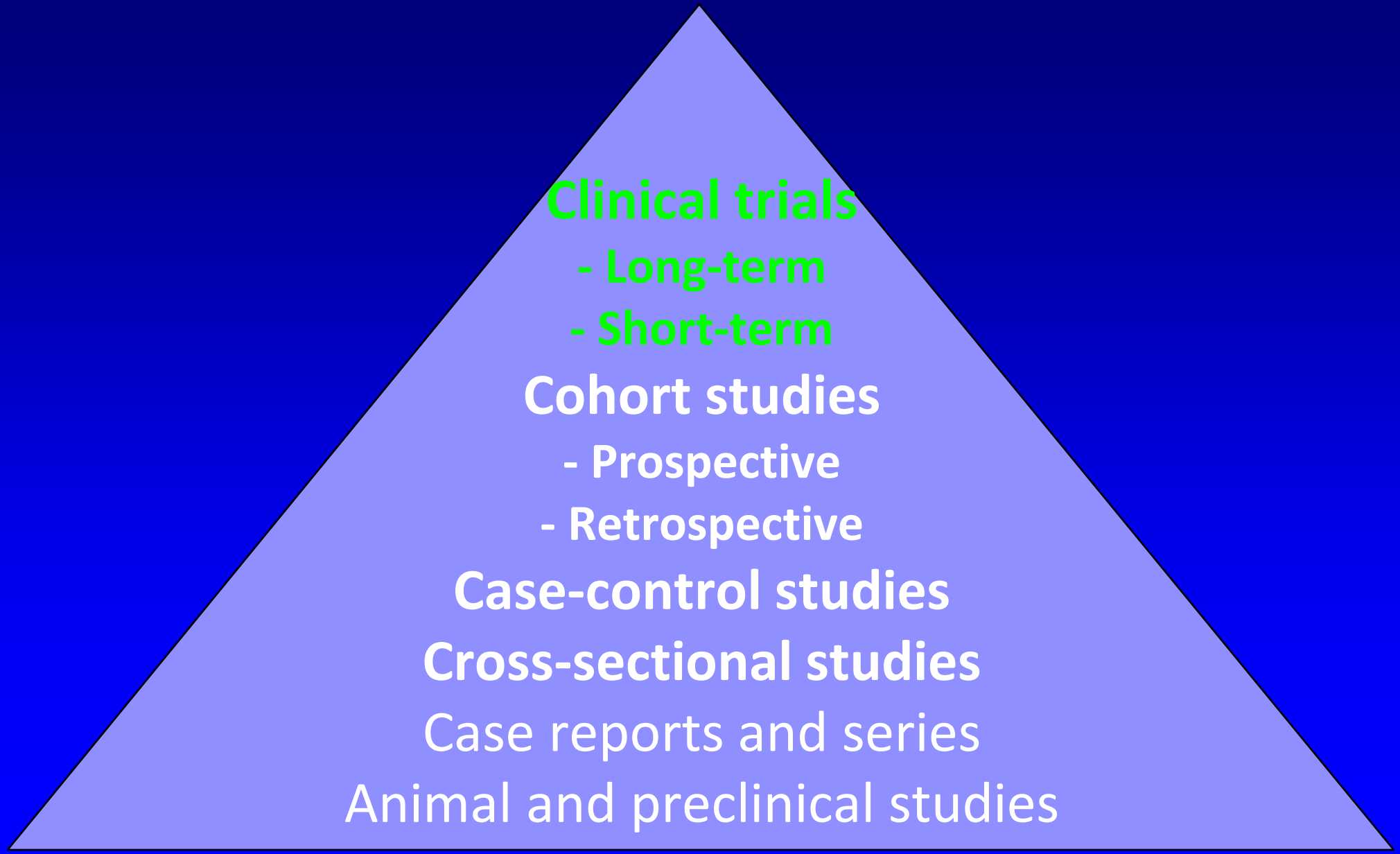
Is it the food?
(Food Matrix)

Is it in combination with other foods?
(Dietary Patterns)

Is it one or more of its nutrients?
(Nutrients or Supplements)

Is it a function of other non-dietary factors?
(Confounding)

Hierarchy of epidemiologic studies



Physicians' Health Study: Who uses supplements?

Baseline Characteristics	Multivitamins only (n=1456)[a]	Multivitamins and other supplements (n=5695)[a]	Other supplements only (n=4748)[a]
Age (years)			
≤65y	1.00 (ref)	1.00 (ref)	1.00 (ref)
66-80	1.23 (1.08-1.39)	1.35 (1.25-1.47)	1.20 (1.11-1.31)
>80	1.98 (1.55-2.54)	1.84 (1.54-2.20)	1.66 (1.38-1.98)
Body mass index (kg/m^2)			
<18.5	1.14 (0.66- 1.97)	0.43 (0.27-0.68)	1.11 (0.77-1.60)
18.5 – 24.9	1.00 (ref)	1.00 (ref)	1.00 (ref)
25 – 29.9	0.89 (0.79-1.01)	0.84 (0.77-0.91)	0.90 (0.83-0.98)
≥30	0.94 (0.77-1.15)	0.76 (0.66-0.87)	0.82 (0.71-0.94)
Smoking status			
Never	1.00 (ref)	1.00 (ref)	1.00 (ref)
Past	1.20 (1.06-1.35)	1.32 (1.22-1.42)	1.14 (1.05-1.23)
Current	1.59 (1.21-2.10)	1.08 (0.87-1.34)	0.95 (0.76-1.18)
Vigorous exercise (≥1 vs. <1/week)	1.09 (0.96-1.22)	1.24 (1.15-1.34)	1.19 (1.10-1.29)
Current aspirin use (yes vs. no)	1.37 (1.21-1.55)	1.87 (1.72-2.02)	1.50 (1.38-1.63)
Cancer	1.13 (0.92-1.38)	1.28 (1.13-1.46)	1.12 (0.98-1.29)
Myocardial infarction and/or stroke	1.13 (0.88-1.45)	0.91 (0.77-1.08)	1.16 (0.98-1.37)
Hypercholesterolemia	1.18 (1.05-1.33)	1.61 (1.49-1.73)	1.40 (1.29-1.51)
Hypertension	1.10 (0.97-1.24)	1.18 (1.09-1.28)	1.16 (1.07-1.25)
Diabetes	0.95 (0.75-1.20)	1.01 (0.87-1.18)	0.95 (0.81-1.11)
Fruits/vegetables (≥5 vs. <5 servings/d)	1.07 (0.95-1.21)	1.29 (1.19-1.40)	1.16 (1.07-1.26)

[a] ORs represent likelihoods as compared to men not using supplements

Rautiainen S, Wang L, Gaziano JM, Sesso HD. Eur J Clin Nutr 2014;53:1065-1072

Physicians' Health Study II

- Large, simple, factorial randomized clinical trial
- Conducted entirely by mail (lower costs)
- 14,641 US male physicians aged ≥50 years
- Tested vitamin E, vitamin C, beta-carotene, and Centrum Silver, a common multivitamin (MVM) used in the US
- 11.2 years of treatment and follow-up through June 1, 2011
  - >164,000 person-years of follow-up
- Primary endpoints:
  - Major cardiovascular events and total cancer
- Secondary endpoints:
  - Individual cardiovascular endpoints and major site-specific cancers
  - Eye disease and cognitive function
- High MVM compliance: 77% @4 yrs, 72% @8 yrs, 67% @end
- *Post-trial follow-up continues*

Table 1. Content of multivitamin (Centrum Silver) tested in PHS II

Vitamin or Mineral	Amount
Vitamin A (50% as β-carotene)	5000 IU
Vitamin C	60 mg
Vitamin D	400 IU
Vitamin E	45 IU
Vitamin K	10 µg
Thiamin	1.5 mg
Riboflavin	1.7 mg
Niacin	20 mg
Vitamin B_6	3 mg
Folic Acid	400 µg
Vitamin B_{12}	25 µg
Biotin	30 µg
Pantothenic Acid	10 mg
Calcium	200 mg
Iron	4 mg
Phosphorus	48 mg
Iodine	150 µg
Magnesium	100 mg
Zinc	15 mg
Selenium	20 µg
Potassium	80 mg

*Other minerals include copper, manganese, nickel, chromium, molybdenum, chloride, boron, silicon, and vanadium

PHS II: β-carotene and cognitive function in men

- 5,956 US male physicians
- Aged ≥65 y
- 50 mg every other day
- 4,052 PHS I participants
  - 18 years of treatment
- 1,904 PHS II participants
  - 1 year of treatment
- General cognition, verbal memory, and category fluency
- Primary endpoint: composite Z score

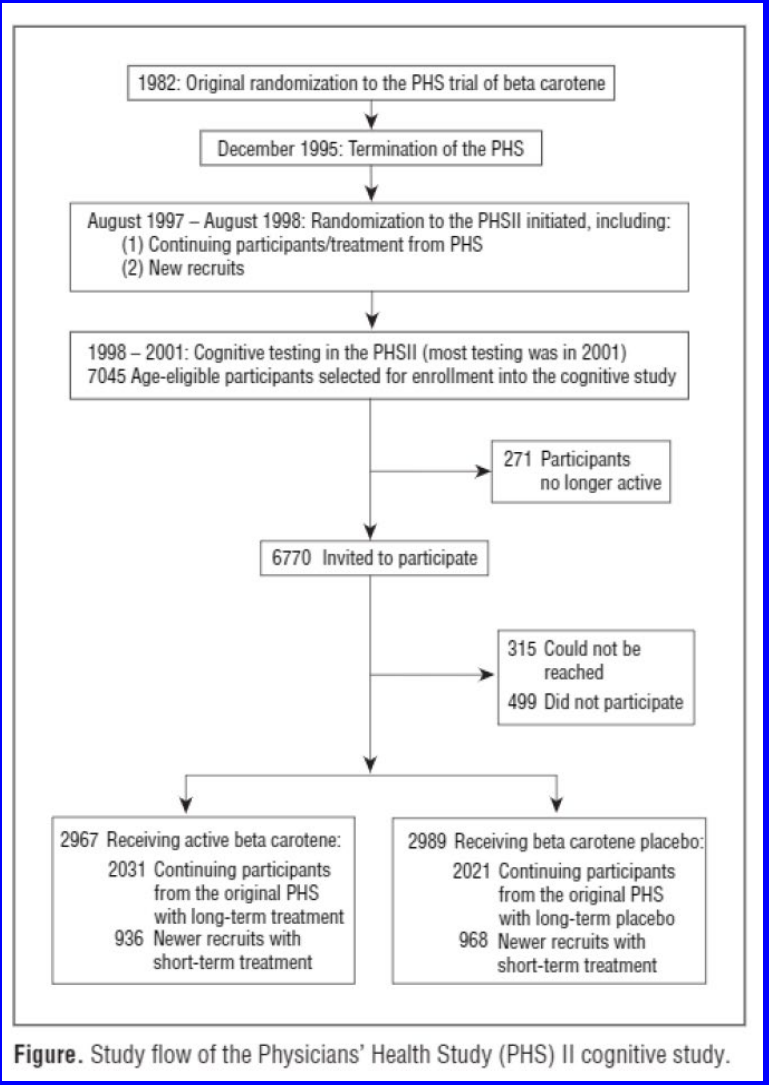


Figure. Study flow of the Physicians' Health Study (PHS) II cognitive study.

Grodstein F et al – Arch Int Med 2007

PHS II: β-carotene and cognitive function in men

Table 3. Mean Cognitive Performance With Short-term Treatment Assignment[a]: the Physicians' Health Study II

Cognitive Measure	Placebo Group (n = 968)	Beta Carotene Group (n = 936)	*P* Value
Global score[b]			
Mean *z* score (SD)[c]	0.007 (0.67)	−0.007 (0.67)	
Mean difference (95% CI)	0 [Reference]	−0.014 (−0.07 to 0.05)	.65
Verbal memory[b]			
Mean *z* score (SD)[c]	0.008 (0.72)	−0.008 (0.72)	
Mean difference (95% CI)	0 [Reference]	−0.015 (−0.08 to 0.05)	.64
TICS[b]			
Mean points (SD)[c]	34.29 (2.64)	34.15 (2.57)	
Mean difference (95% CI)	0 [Reference]	−0.13 (−0.37 to 0.10)	.26
Category fluency[b]			
Mean points (SD)[c]	20.09 (6.15)	20.02 (6.14)	
Mean difference (95% CI)	0 [Reference]	−0.06 (−0.62 to 0.49)	.82

Abbreviations: CI, confidence interval; TICS, Telephone Interview of Cognitive Status.

[a]Short-term treatment is a mean of 1 year among subjects newly recruited to the Physicians' Health Study II.

Table 4. Mean Cognitive Performance With Long-term Treatment Assignment[a]: the Physicians' Health Study II

Cognitive Measure	Placebo Group (n = 2021)	Beta Carotene Group (n = 2031)	*P* Value
Global score[b]			
Mean *z* score (SD)[c]	−0.024 (0.71)	0.023 (0.69)	
Mean difference (95% CI)	0 [Reference]	0.047 (0.00 to 0.09)	.03
Verbal memory[b]			
Mean *z* score (SD)[c]	−0.032 (0.74)	0.031 (0.73)	
Mean difference (95% CI)	0 [Reference]	0.063 (0.02 to 0.11)	.007
TICS[b]			
Mean points (SD)[c]	34.23 (2.80)	34.41 (2.73)	
Mean difference (95% CI)	0 [Reference]	0.18 (0.01 to 0.35)	.04
Category fluency[b]			
Mean points (SD)[c]	20.04 (6.04)	20.03 (5.94)	
Mean difference (95% CI)	0 [Reference]	−0.012 (−0.38 to 0.35)	.95

Abbreviations: CI, confidence interval; TICS, Telephone Interview of Cognitive Status

[a]Long-term treatment is a mean of 18 years among subjects continuing from the original Physicians' Health Study.

Grodstein F et al – Arch Int Med 2007

PHS II: Multivitamins and cognitive function in men

Table 2. Mean (SD) Cognitive Test Scores at Initial Assessment*

Cognitive Test	Multivitamin Group (n = 2980)	Placebo Group (n = 2967)
Global composite (Z score), *SU*	0.01 (0.7)	−0.005 (0.7)
Verbal memory composite (Z score), *SU*	0.00 (0.7)	−0.005 (0.7)
TICS	34.3 (2.7)	34.3 (2.7)
EBMT		
Immediate recall	9.7 (1.9)	9.7 (1.9)
Delayed recall	9.4 (2.1)	9.3 (2.2)
Delayed recall of 10-word list	2.6 (2.0)	2.6 (2.0)
Category fluency	20.1 (6.0)	20.0 (6.1)

EBMT = East Boston Memory Test; TICS = Telephone Interview for Cognitive Status.
* Initial cognitive testing was conducted at a mean of 2.5 y (range, 0.18–5.3 y) after randomization.

Table 4. Mean Difference in Cognitive Decline Between Multivitamin and Placebo Groups

Cognitive Test	Mean Difference in Cognitive Decline Between Multivitamin and Placebo Groups (95% CI)*	*P* Value
Global composite score†		
From initial cognitive assessment to:		
Second cognitive assessment	−0.02 (−0.05 to 0.02)	0.28
Third cognitive assessment	0.01 (−0.04 to 0.05)	0.79
Fourth cognitive assessment	0.01 (−0.05 to 0.06)	0.77
Average over follow-up	−0.01 (−0.04 to 0.02)	0.53
Verbal memory composite score†		
From initial cognitive assessment to:		
Second cognitive assessment	−0.02 (−0.06 to 0.02)	0.43
Third cognitive assessment	0.01 (−0.03 to 0.06)	0.57
Fourth cognitive assessment	0.01 (−0.05 to 0.07)	0.84
Average over follow-up	−0.005 (−0.04 to 0.03)	0.80
TICS score		
From initial cognitive assessment to:		
Second cognitive assessment	0.04 (−0.10 to 0.18)	0.59
Third cognitive assessment	−0.04 (−0.21 to 0.13)	0.64
Fourth cognitive assessment	0.07 (−0.18 to 0.32)	0.59
Average over follow-up	0.02 (−0.11 to 0.15)	0.79
Category fluency score		
From initial cognitive assessment to:		
Second cognitive assessment	−0.22 (−0.52 to 0.09)	0.165
Third cognitive assessment	0.05 (−0.30 to 0.40)	0.77
Fourth cognitive assessment	0.22 (−0.21 to 0.65)	0.31
Average over follow-up	−0.07 (−0.35 to 0.20)	0.59

Grodstein F et al – Ann Int Med 2013

Multivitamin supplementation and brain health

- 60 women aged 25-45 years who experienced psychological distress
- Placebo-controlled randomized clinical trial
- Multivitamin (B vitamins, biotin, folic acid, vitamin D, Mg, Zn, winter cherry extract)
- 8 week intervention
- Primary outcomes: Changes in anxiety, curiosity, depression, and anger (Spielberger's State-Trait Personality Inventory) **[no effect]**
- Proinflammatory biomarkers **[reductions in TNF-β, TNF-α, and IL-1]**

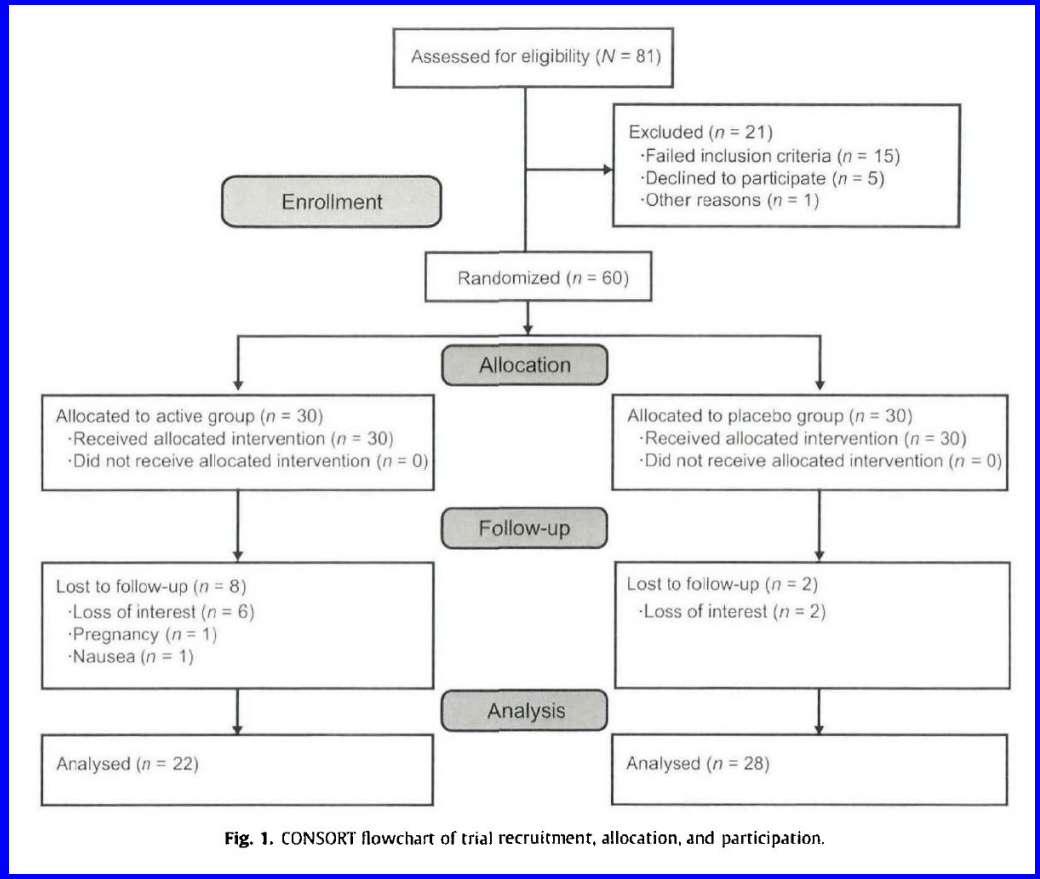
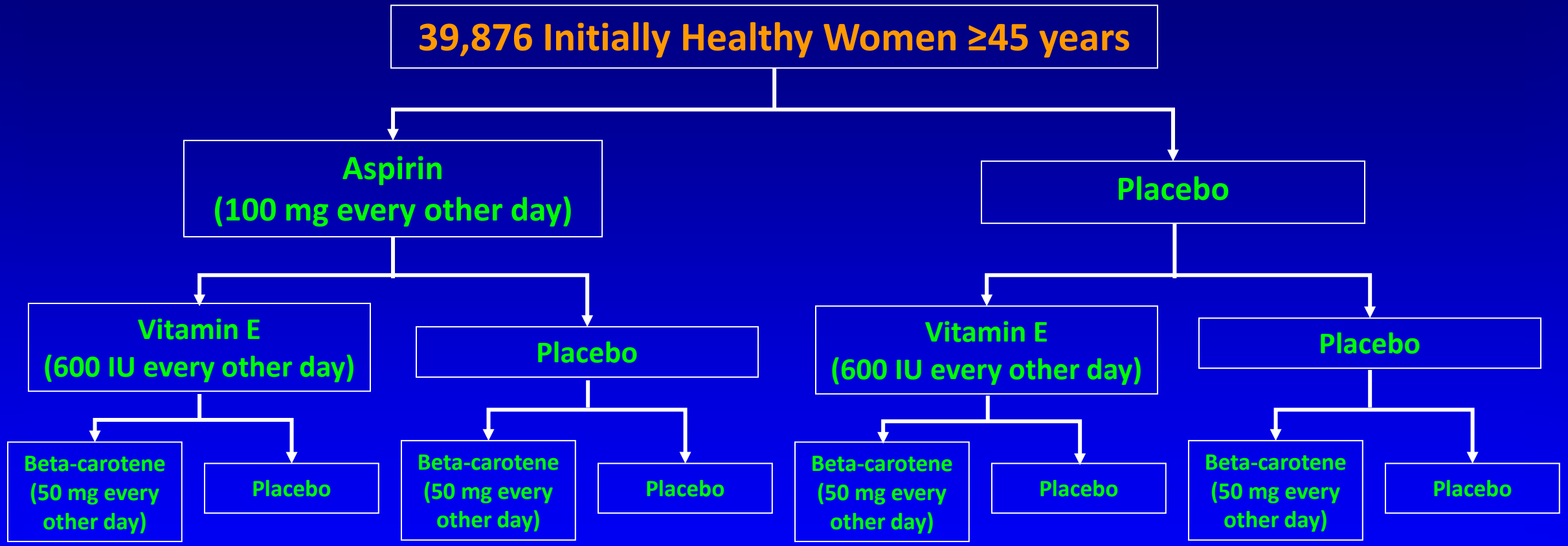


Fig. 1. CONSORT flowchart of trial recruitment, allocation, and participation.

Oliver-Baxter JM et al – J Integrative Med 2018

Women's Health Study (WHS)



Mean Treatment Period = 10 years; *ended 2004; observational follow-up continues*

Primary Outcomes: Total cancer and Major cardiovascular events (MI, stroke, CVD death)

Baseline Blood Collection: 28,345 (71%) participants; Women's Genome Health Study; biomarkers

Rexrode KM *et al*. J Women's Health Gend Based Med 2000

WHS: Vitamin E and cognitive function

- 6,377 women aged ≥65 y
- 600 IU vitamin E every other day (as α-tocopherol acetate)
- Three cognitive assessments every 2 years starting 5.6 years after randomization
- General cognition, verbal memory, and category fluency
- Primary endpoint: composite Z score
- Also considered substantial decline

Table 5. Relative Risk of Substantial Decline*

Cognitive Test	Substantial Decline, RR (95% CI)	*P* Value
Primary end point: global score†		
Placebo group	1.00	.36
Vitamin E group	0.92 (0.77-1.10)	
Key secondary end point: verbal memory score†		
Placebo group	1.00	.08
Vitamin E group	0.85 (0.71-1.02)	
TICS†		
Placebo group	1.00	.82
Vitamin E group	0.98 (0.83-1.16)	
Category fluency†		
Placebo group	1.00	.23
Vitamin E group	1.12 (0.93-1.35)	

Abbreviations: CI, confidence interval; RR, relative risk; TICS, Telephone Interview of Cognitive Status.

*Substantial decline is defined as the worst 10% of the distribution of decline from the first to third assessment (global score, –0.8 points; verbal memory score, –0.9 points; TICS score, –4 points; and category fluency, –7 points). Adjusted for time between first and third cognitive interview.

†Verbal score is a composite score of the immediate and delayed recalls of both the TICS 10-word and the East Boston Memory Test; global score is a composite score of TICS, immediate and delayed recalls of the East Boston Memory Test, category fluency, and delayed recall of the TICS 10-word list.

Kang JH et al – Arch Int Med 2006

Women's Antioxidant Cardiovascular Study (WACS): Vitamin E, vitamin C, and β-carotene and cognitive function

- 2,824 US women aged ≥65 y with or at high risk of cardiovascular disease
- 2x2x2 factorial placebo-controlled trial testing:
  - 402 mg vitamin E every other day
  - 50 mg β-carotene every other day
  - 500 mg/d vitamin C
- 4 telephone-based assessments over 5.4 y
  - First assessment 3.5 y into the trial

Table 2. Mean Difference in Cognitive Function at Each Cognitive Assessment for Each Antioxidant

		Vitamin E		Vitamin C		β-Carotene	
Cognitive Assessment	n	Mean Difference in Score, Active Group−Placebo Group (95% CI)*	*P*	Mean Difference in Score, Active Group−Placebo Group (95% CI)*	*P*	Mean Difference in Score, Active Group−Placebo Group (95% CI)*	*P*
Primary endpoint: Global score† (difference in score associated with being 1 y older=−0.03)							
1	2824	−0.01 (−0.06–0.04)	0.71	0.05 (0.00–0.10)	0.05	−0.03 (−0.08–0.02)	0.19
2	2511	0.00 (−0.06–0.06)	0.94	0.05 (−0.01–0.11)	0.09	0.00 (−0.06–0.05)	0.89
3	2271	−0.02 (−0.09–0.05)	0.55	0.05 (−0.01–0.12)	0.10	0.01 (−0.06–0.07)	0.82
4	1586	−0.05 (−0.13–0.02)	0.17	0.13 (0.06–0.20)	0.0005	−0.01 (−0.09–0.06)	0.71
Key secondary endpoint: Verbal memory score† (difference in score associated with being 1 y older=−0.03)							
1	2824	0.02 (−0.03–0.07)	0.43	0.05 (0.00–0.10)	0.06	−0.01 (−0.07–0.04)	0.62
2	2511	0.02 (−0.04–0.09)	0.45	0.05 (−0.01–0.11)	0.13	0.00 (−0.06–0.06)	0.99
3	2271	−0.01 (−0.08–0.06)	0.75	0.07 (0.00–0.13)	0.05	0.02 (−0.04–0.09)	0.50
4	1586	−0.06 (−0.13–0.02)	0.13	0.14 (0.06–0.21)	0.0004	−0.02 (−0.09–0.06)	0.68
TICS score† (difference in score associated with being 1 y older=−0.13)							
1	2824	−0.01 (−0.25–0.23)	0.95	0.16 (−0.08–0.39)	0.20	−0.18 (−0.42–0.06)	0.14
2	2511	0.03 (−0.23–0.29)	0.80	0.15 (−0.11–0.41)	0.24	0.06 (−0.20–0.32)	0.63
3	2270	−0.08 (−0.37–0.21)	0.61	0.15 (−0.14–0.44)	0.31	0.14 (−0.15–0.43)	0.35
4	1586	−0.16 (−0.49–0.16)	0.33	0.46 (0.14–0.78)	0.006	−0.13 (−0.46–0.19)	0.42
Category fluency score (difference in score associated with being 1 y older=−0.18)							
1	2819	−0.42 (−0.78–−0.06)	0.02	0.03 (−0.33–0.39)	0.87	−0.22 (−0.58–0.14)	0.23
2	2504	−0.45 (−0.83–−0.06)	0.02	0.03 (−0.36–0.41)	0.90	−0.05 (−0.44–0.34)	0.80
3	2261	−0.25 (−0.66–0.16)	0.24	0.05 (−0.36–0.46)	0.80	−0.05 (−0.46–0.36)	0.80
4	1583	−0.35 (−0.80–0.10)	0.13	0.25 (−0.20–0.70)	0.27	−0.01 (−0.46–0.44)	0.96

*From longitudinal linear models of adjusted mean cognitive performance.

†Verbal score is a composite score of the z scores of the immediate and delayed recalls of both the TICS 10-word and the East Boston Memory Test; global score is a composite score of the z scores of TICS, immediate and delayed recalls of the East Boston Memory Test, category fluency, and delayed recall of the TICS 10-word list.

Kang JH et al – Circulation 2009

Women's Health Initiative: 400 IU/d vitamin D + 1000 mg/d calcium and dementia or mild cognitive impairment

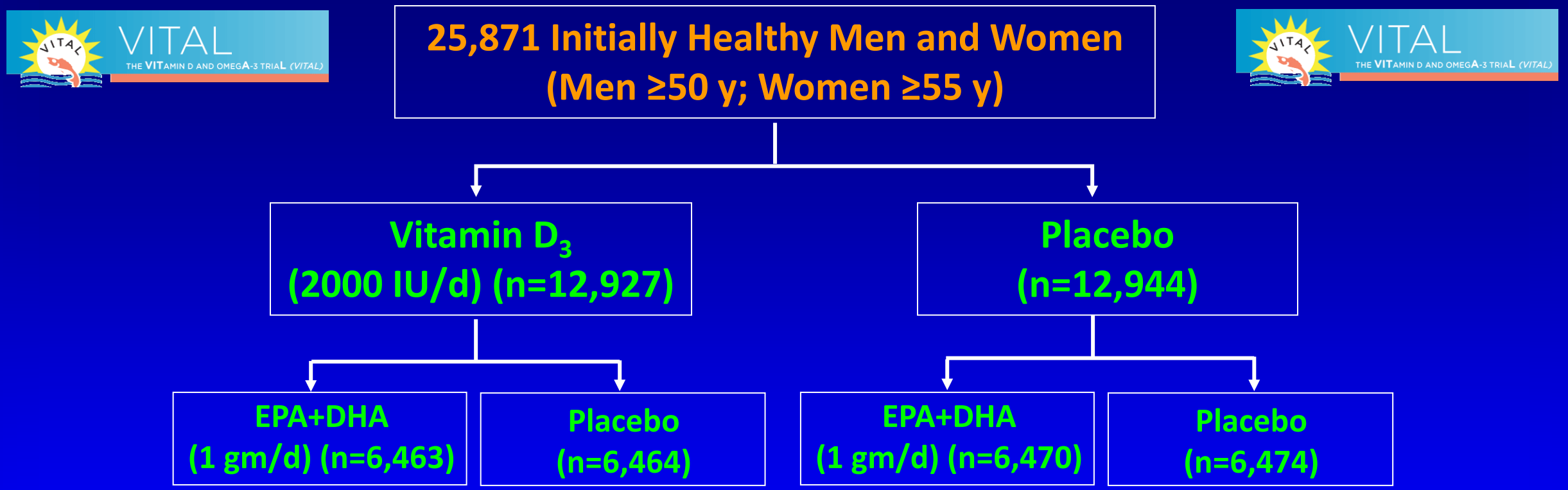
Incidence of Probable Dementia or Mild Cognitive Impairment (MCI) by Treatment Assignment

	Calcium/Vitamin D N=2034	Placebo N=2109	HR (95% CI)
Intent-to Treat Analysis			
Probable Dementia or Mild Cognitive Impairment, No. (%)	98 (4.8%)	108 (5.1%)	0.94 (0.72, 1.24) P=0.68
Follow-up, mean, years (± SD)	7.7 (± 2.5)	7.8 (± 2.5)	
Rate per 10,000 person-years	62.2	65.9	
Analysis Excluding Follow-Up Time for Non-Adherent Participants[a]			
Probable Dementia or Mild Cognitive Impairment, No. (%)	62 (3.1%)	62 (2.9%)	1.05 (0.74, 1.49) P=0.79
Follow-up, mean, years (± SD)	6.4 (± 1.7)	6.44 (± 1.6)	
Rate per 10,000 person-years	48.0	45.7	

[a]Participants excluded 6 months after nonadherence detected

Rossom RC et al – J Am Geriatr Soc 2012

*VIT*amin D and Omeg*A*-3 Tria*L* (VITAL)



Median Treatment Period = 5.3 years; *treatment ended Dec 2017; follow-up continues*

Primary Outcomes: Total cancer and major cardiovascular events (MI, stroke, CVD death)

Baseline Blood Collection: 16,787 participants; follow-up samples at 1, 2, and/or 4 years in a subgroup

Baseline Clinic Visit: 1,054 Boston-based participants; follow-up visits at 2 and/or 4 years in a subgroup

Ancillary Studies: More than 20, on a variety of study outcomes

Manson JE *et al*. N Engl J Med 2018

VITAL Cognition

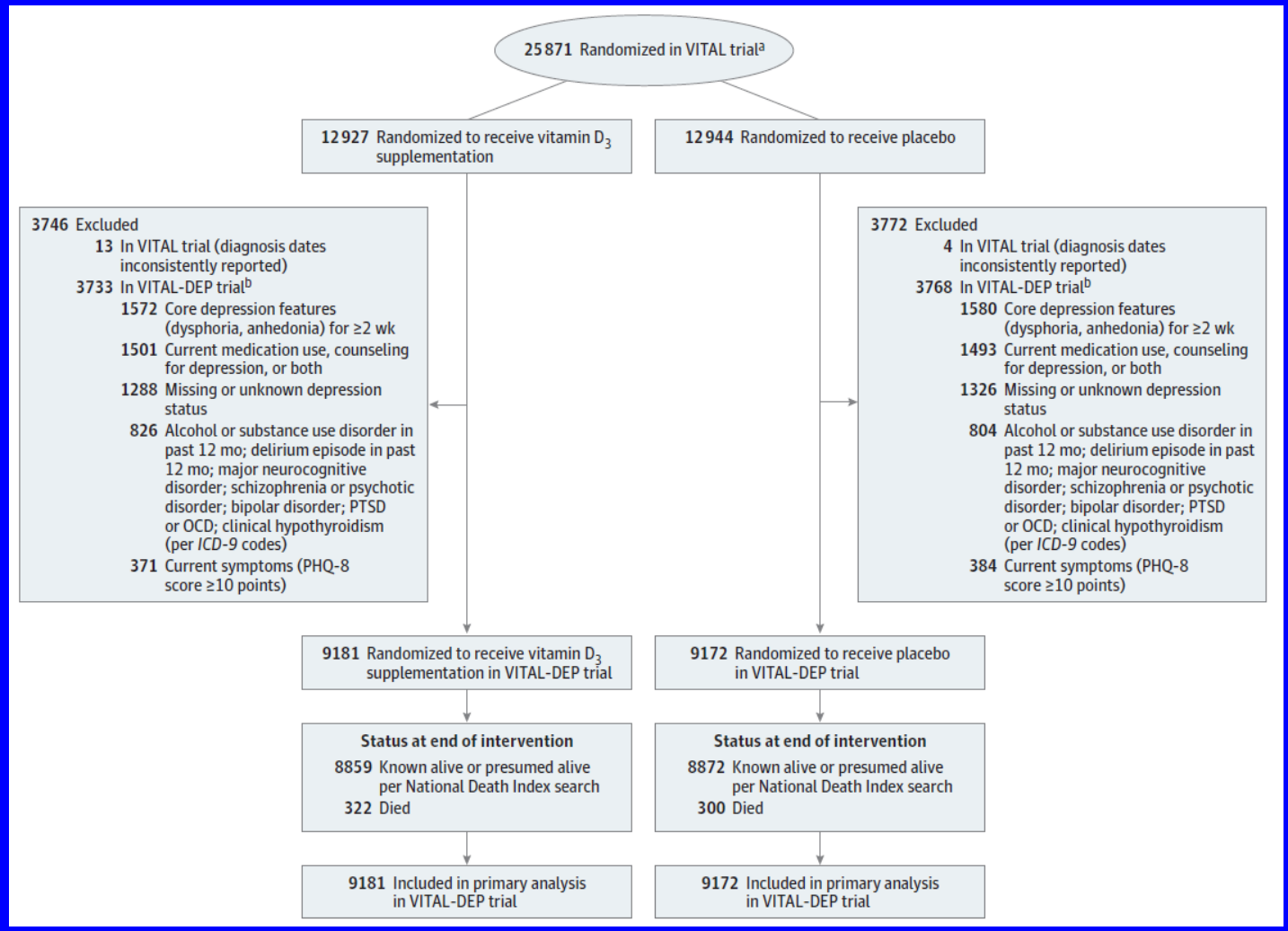
- Ancillary study of 3,992 VITAL participants
- Aged ≥60 years with no hearing impairment
- Telephone-based cognitive assessments
- Examining 2000 IU/day vitamin D and 840 mg/day fish oil
- Primary outcome: Global composite score of 7 tests (e.g. TICS, EBMT)
- Results expected later in 2021

Micronutrients and Depression in Older Adults

- VITATOPS trial: Depression substudy (Almeida et al 2010)
  - 50% reduction in risk of major depression among 273 patients (mean age 63 y) with recent stroke or transient ischemic attack who received a daily folic acid (2 mg)/vitamin B_6 (25 mg)/vitamin B_{12} (0.5 mg) combination over a 7.1-year average follow-up period.
- Trial of 299 men aged ≥75 y with hypertension (Ford et al 2008)
  - No significant differences in depressive symptoms or incidence of clinically significant depression comparing combined folic acid (2 mg/d), B_6 (25 mg/d) and B_{12} (400 mg/d) to placebo over 2 y.
- Trial of 909 community-based older adults aged 60 to 74 y (Walker et al 2010)
  - No differences in depressive symptoms comparing combined folic acid (400 mg/d) and B12 (100 mg/d) to placebo over 2 y .
- SU.FOL.OM3 trial substudy (Andreeva et al 2012)
  - No differences in depressive symptoms by allocation to B vitamins (0.56 mg/d 5-methyl-tetrahydrofolate and vitamins B_6 (3 mg/d) and B_{12} (0.02mg/d)) versus placebo among 2000 CVD survivors aged 45–80 years after a median treatment duration of 4.7 y.

VITAL: Vitamin D and depression

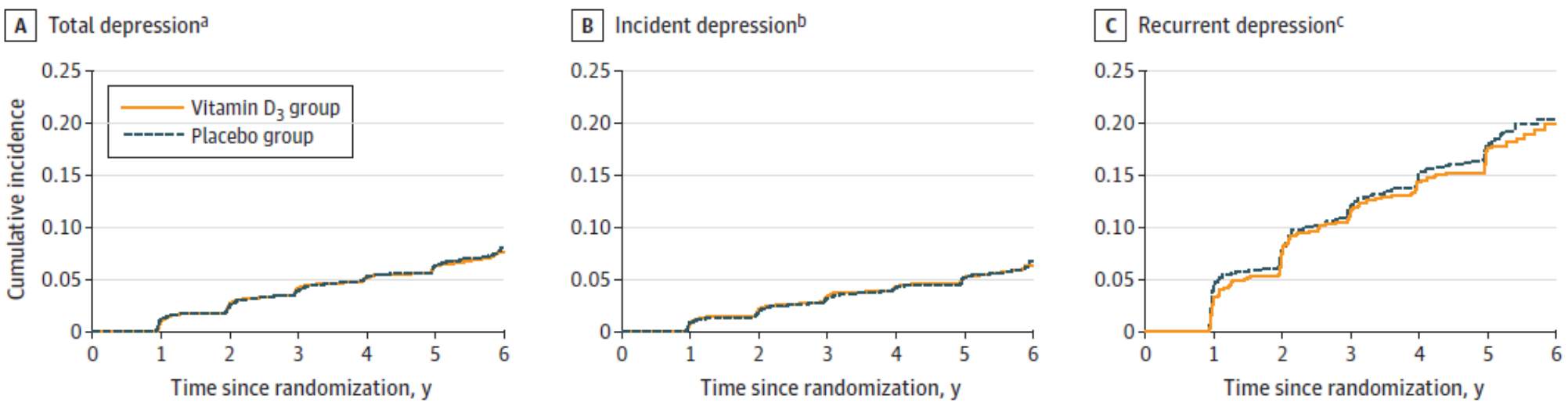
- 18,353 US men and women
  - 1,696 with history of depression
  - 16,657 with no history of depression
- Mean age, 67.5 years
- Tested in a 2x2 factorial trial:
  - 2000 IU/d vitamin D_3
  - Fish oil
- 5.3 years of treatment and follow-up
- Primary endpoint: Risk of incident depression or depressive symptoms (1234 cases)



Okereke OI et al. JAMA 2020

VITAL: Vitamin D and depression

Figure 2. Cumulative Incidence Since Randomization Until Occurrence of Primary and Secondary Outcomes



No. at risk

Vitamin D_3	9181	9059	8865	8674	8447	6806	614
Placebo	9172	9038	8886	8699	8437	6767	586

Vitamin D_3	8350	8257	8105	7948	7757	6257	563
Placebo	8307	8213	8089	7940	7713	6192	543

Vitamin D_3	831	802	760	726	690	549	51
Placebo	865	825	797	759	724	575	43

Panels B and C are provided to illustrate the cumulative incidence curves for incidence and recurrence separately from the total (panel A).

[a] Sum of incidence and recurrence of depression or clinically relevant depressive symptoms. This is the primary outcome.

[b] Among the 16 657 participants without a history of depression at baseline. This is a secondary outcome.

[c] Among the 1696 participants with a history of depression at baseline who were not receiving treatment within the past 2 years. This is a secondary outcome.

Okereke OI et al. JAMA 2020

Women's Health Initiative: 400 IU/d vitamin D + 1000 mg/d calcium and depression

Table 3. Association of Calcium and Vitamin D Supplementation With Risk of Depressive Symptoms Above the Threshold Level at Year 3 and Risk of Antidepressant Medication Use at Year 3, Women's Health Initiative Calcium and Vitamin D Trial, 1995–2003

	All Participants				Participants Without Evidence of Depression at Year 1[a]			
	No. of Cases	No. of Noncases	Multivariate OR[b]	95% CI	No. of Cases	No. of Noncases	Multivariate OR[c]	95% CI
Depressive symptoms above threshold level (Burnam score ≥0.06) at year 3								
Supplementation group	119	997	1.16	0.86, 1.56	70	886	1.41	0.97, 2.05
Placebo group	108	1,039	1	Referent	52	949	1	Referent
Use of antidepressant medication at year 3								
Supplementation group	1,326	15,732	1.01	0.92, 1.12	419	14,248	0.96	0.84, 1.10
Placebo group	1,380	15,597	1	Referent	428	14,001	1	Referent

Abbreviations: CI, confidence interval; OR, odds ratio; WHI, Women's Health Initiative.

[a] Analysis excluded women with depressive symptoms above the threshold level (Burnam score ≥0.06) or antidepressant use at baseline.

[b] Multivariable models adjusted for age, race/ethnicity, WHI Hormone Trial intervention, and WHI Dietary Modification Trial intervention. The analysis of risk of depressive symptoms above the threshold level (Burnam score ≥0.06) included adjustment for this variable at baseline. The analysis of risk of antidepressant use included adjustment for antidepressant use at baseline.

[c] Multivariable models adjusted for age, race/ethnicity, WHI Hormone Trial intervention, and WHI Dietary Modification Trial intervention.

Bertone-Johnson ER et al – Am J Epidemiol 2012

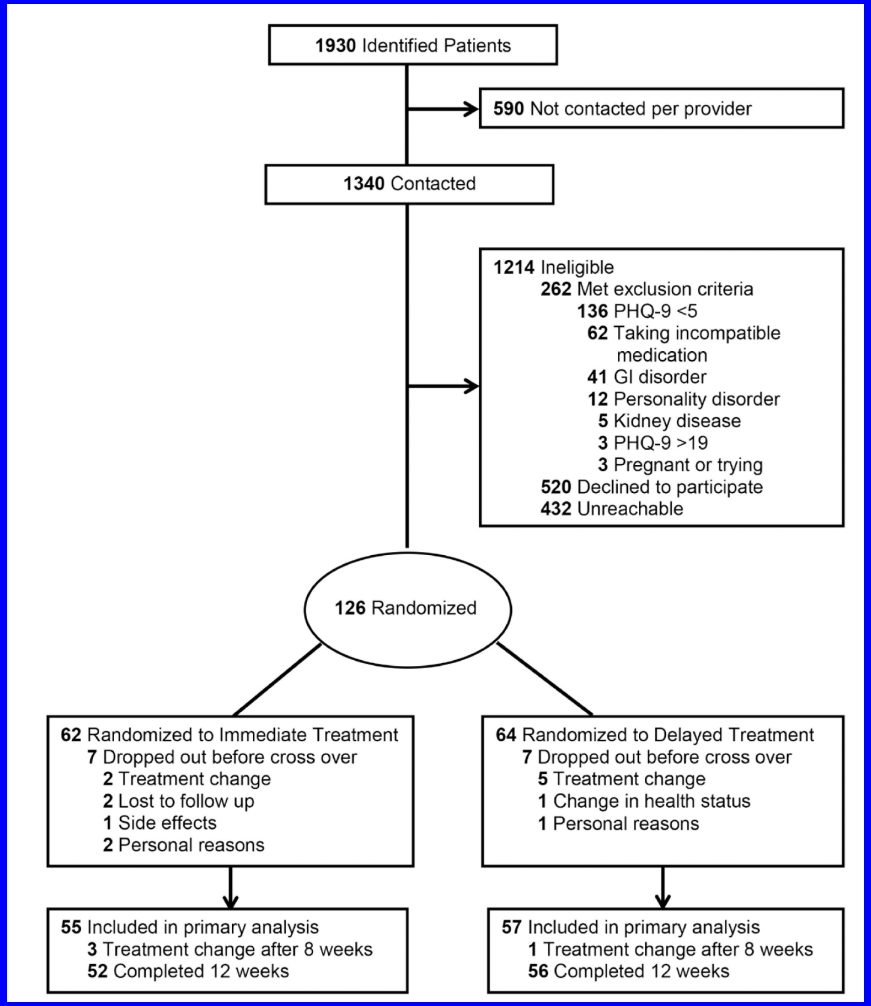
Other trace minerals with potential linkages to depression and depressive symptomology

- Zinc
  - Increased cortisol
  - Decreased neurogenesis and neural plasticity
  - Disruption of glutamate homeostasis
- Selenium
  - Dysregulation of thyroid function and oxidative pathways
  - Inflammatory pathways
- Magnesium
  - Dysregulation of hypothalamic–pituitary–adrenal (HPA axis)
  - Increased calcium in brain
  - Inflammatory pathways

Wang J et al. Nutrients 2018

Trial of magnesium supplementation and changes in depression and anxiety symptomology

- Crossover trial of 126 adults aged ≥18 y (mean, 52 y) with diagnosed depression or mild-to-moderate depressive symptomology via PHQ-9
- 248 mg/day magnesium chloride
- 12 weeks total; open label; 2 6-week interventions
- Primary outcome: Changes in depressive symptoms
- Secondary outcome: Changes in anxiety symptoms



Tarleton EK et al. PLoS ONE 2017

Trial of magnesium supplementation and changes in depression and anxiety symptomology

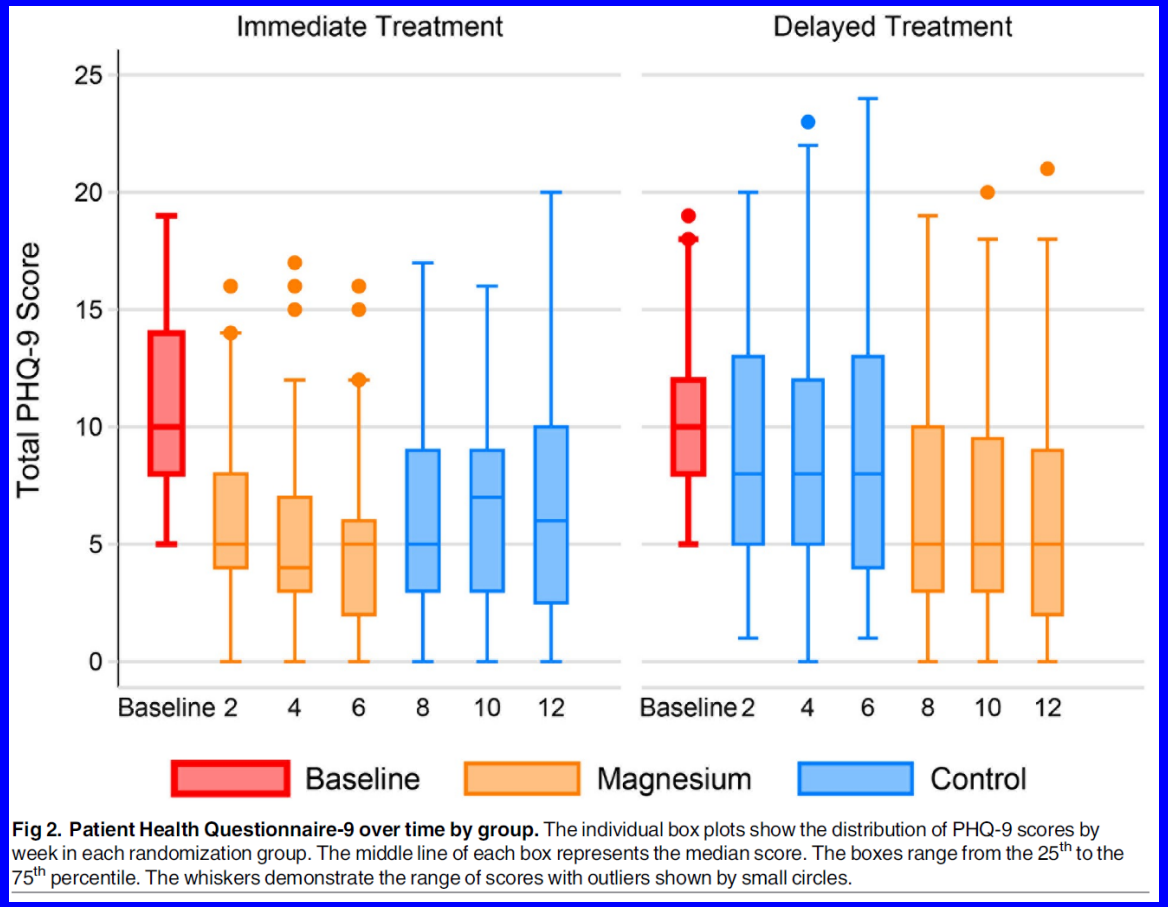


Fig 2. Patient Health Questionnaire-9 over time by group. The individual box plots show the distribution of PHQ-9 scores by week in each randomization group. The middle line of each box represents the median score. The boxes range from the 25th to the 75th percentile. The whiskers demonstrate the range of scores with outliers shown by small circles.

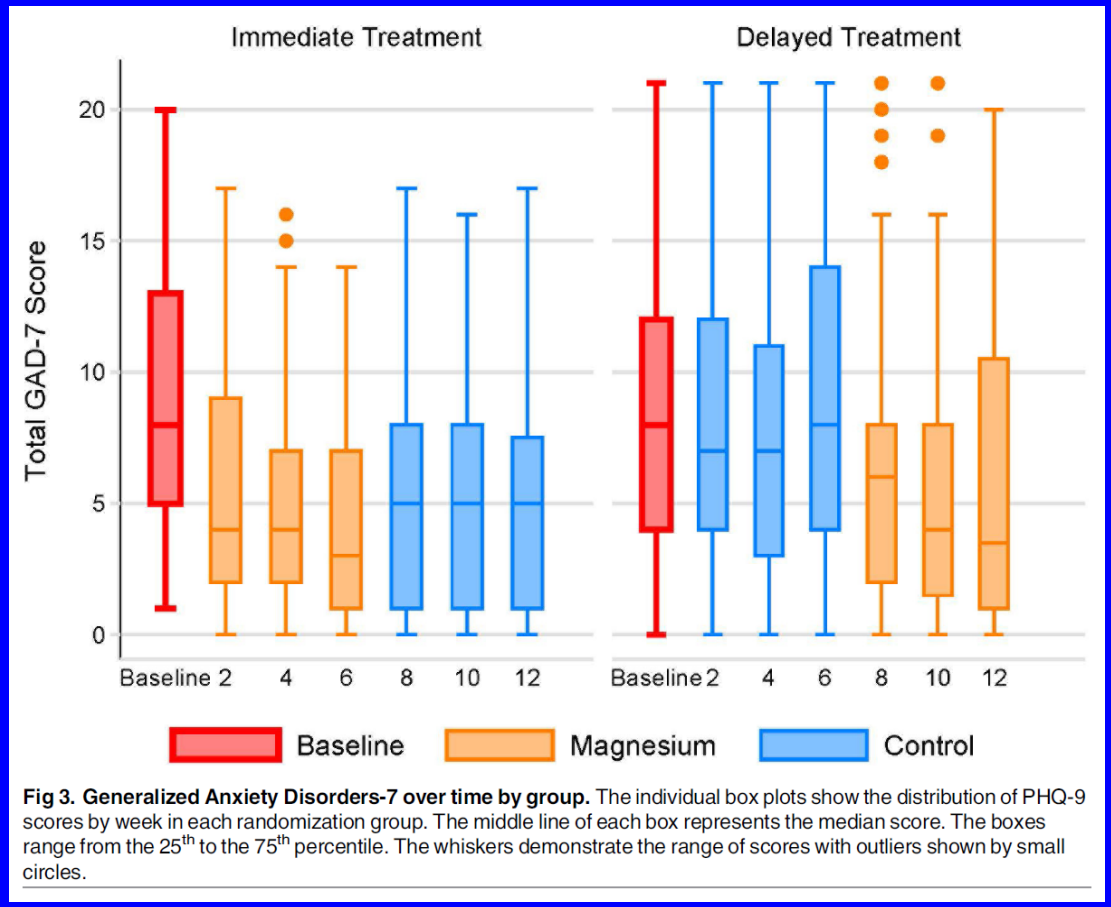


Fig 3. Generalized Anxiety Disorders-7 over time by group. The individual box plots show the distribution of PHQ-9 scores by week in each randomization group. The middle line of each box represents the median score. The boxes range from the 25th to the 75th percentile. The whiskers demonstrate the range of scores with outliers shown by small circles.

Depression

Anxiety

Tarleton EK et al. PLoS ONE 2017

Magnesium, vitamin B_6 and stress in healthy adults

- 268 French adults aged 18-50 years with moderate to extremely severe stress at baseline
- 8-week trial comparing 300 mg/day Mg + 30 mg/day vitamin B_6 versus Mg alone
  - Why not placebo control?
- Primary outcome: Changes in stress at 8 weeks

Table 3. Change in DASS-42 stress subscale score from baseline to Week 4 and to Week 8.

mITT population	**Mg–vit B6 combination (N = 132)**	**Mg (N = 132)**
Change from baseline to Week 4[a] (95% CI)	−8.94 (−10.22 to −7.65)	−7.58 (−8.86 to −6.30)
Difference between treatment arms	1.35 (−0.36 to 3.06), p = 0.1203	
Change from baseline to Week 8[a] (95% CI)	−12.44 (−13.83 to −11.05)	−11.72 (−13.10 to −10.33)
Difference between treatment arms	0.72 (−1.15 to 2.59), p = 0.4472	
PP population	**Mg–vit B6 combination (N = 117)**	**Mg (N = 116)**
Change from baseline to Week 4[ab] (95% CI)	−9.59 (−11.03 to −8.15)	−8.04 (−9.45 to −6.63)
Difference between treatment arms	1.55 (−0.33 to 3.43), p = 0.1056	
Change from baseline to Week 8[ab] (95% CI)	−13.26 (−14.81 to −11.71)	−12.21 (−13.73 to −10.68)
Difference between treatment arms	1.06 (−0.99 to 3.10), p = 0.3095	

[a]Difference from baseline in adjusted mean.

[b]Subjects with subscale scores ≤18 baseline were excluded from the PP population.

CI, confidence interval; DASS, Depression Anxiety Stress Scale; mITT, modified intention-to-treat; Mg, magnesium; PP, per protocol; Vit B6, vitamin B6.

Pouteau E et al – PLoS One 2018

Lutein and cognition in adults

- Systematic review of 5 placebo-controlled trials of lutein (10-12 mg/d) in adults with no baseline cognitive impairment and 4-12 months treatment
- Lutein supplementation has shown consistent selective improvements of visual episodic memory in young and middle-aged adults and inhibition in middle-aged and older adults
- Cognitive function is multidimensional and it can be challenging to connect trials and results

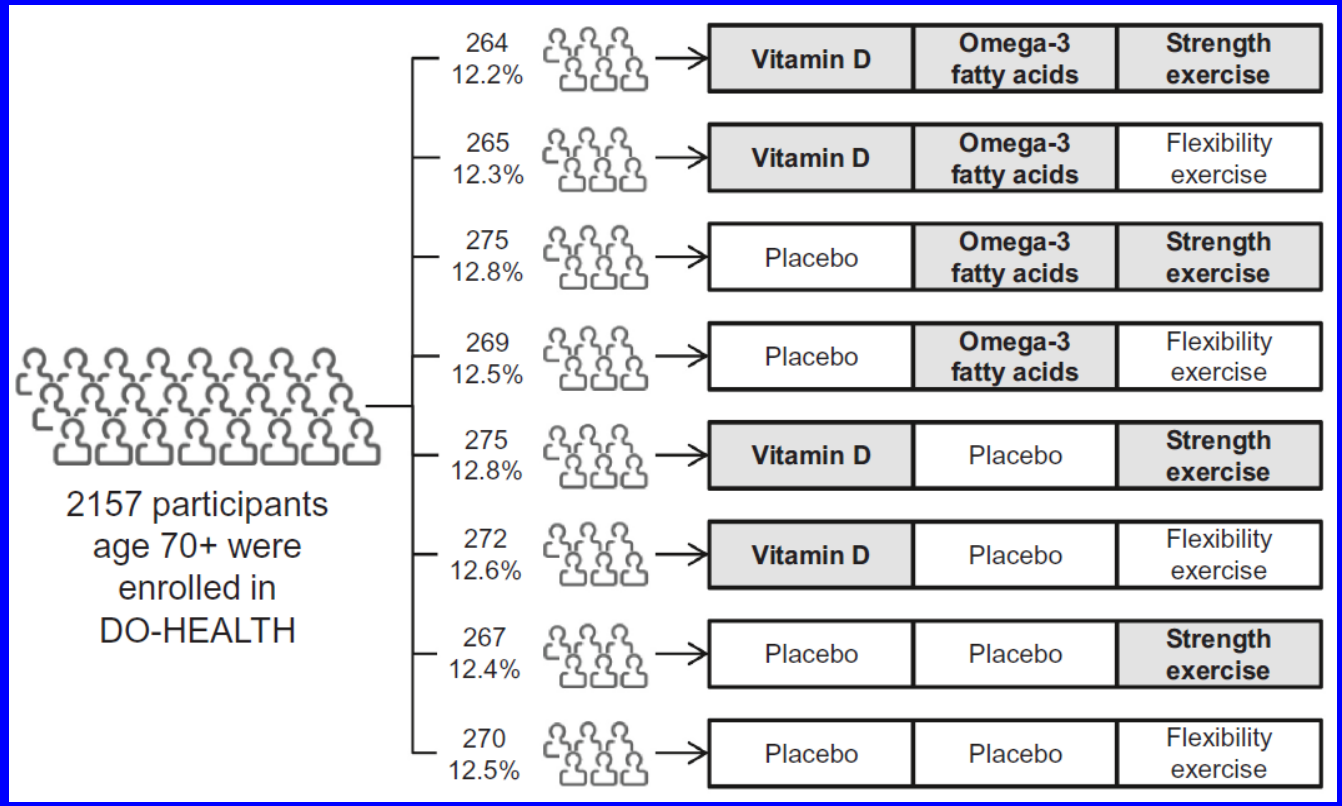
Table 1. Characteristics of included studies.

Lead Author; Year; Country	Study Design, Duration	Sample size (Female)	Age (mean ± SD)	Health Status	Cognitive Status	Intervention (Timing or Method)	Control (Contents)
Power; 2018; Ireland	A parallel-group, double-blind, placebo-controlled, block-randomized clinical trial, 12 months	91 (48%) P: 46 A: 45	P: 46.43 ± 13.21 A: 44.38 ± 11.57	Low MP volume without the retinal disease, no consumption of L and/or Z and/or MZ supplement	No impairment	L: 10 mg/d MZ: 10 mg/d Z: 2 mg/d (with a meal)	Placebo (capsule containing sunflower oil)
Lindberg; 2017; USA	A single-site, double-blind RCT, 12 months	44 (59%) P: 14 A: 30	P: 70.43 ± 5.43 A: 72.43 ± 6.48	Community-dwelling older adults, good overall health, no consumption of xanthophyll supplement	*n*/R	L: 10 mg/d Z: 2 mg/d (*n*/R)	Placebo (*n*/R)
Renzi-Hammond; 2017; USA	A randomized, double-masked, placebo-controlled trial, 12 months	51 (43%) P: 14 A: 37	P: 20.5 ± 1.91 A: 21.5 ± 2.69	Healthy young college students, no consumption of the supplement	No impairment	L: 10 mg/d Z: 2 mg/d (with the highest fat meal)	Placebo (*n*/R)
Hammond; 2017; USA	The double-masked, randomized, placebo-controlled trial, 12 months	51 (59%) P: 15 A: 36	P: 70.93 ± 5.70 A: 72.51 ± 6.24	Healthy community-dwelling older adults, no consumption of L&Z supplement	No impairment	L: 10 mg/d Z: 2 mg/d (with the highest fat meal)	Placebo (*n*/R)
Johnson; 2008; USA	Randomized, double-blind, intervention trial, 4 months	49 (100%) P: 10 D: 14 L: 11 D+L: 14	P: 68.0 ± 1.2 D: 68.5 ± 1.3 L: 66.7 ± 1.9 D+L: 68.6 ± 1.3	Healthy, non-smoking older women, no consumption of carotenoids supplement	No impairment	L: 12 mg/d (with nutritional energy drink)	Placebo (*n*/R)

Nouchi R *et al* – Nutrients 2020

DO-HEALTH:
A new clinical trial on nutrition and brain health

- European multi-center trial
- 2x2x2 factorial trial
  - 2000 IU/d vitamin D
  - 1000 mg/d omega-3 fatty acids (1:2 EPA:DHA)
  - 3 days/wk strength/flexibility home exercise
- 3 years follow-up
- Relevant outcomes
  - Cognitive decline
  - Mental health
  - Depression
  - Gait/physical performance



https://clinicaltrials.gov/ct2/show/NCT01745263

Bischoff-Ferrari HA *et al*. Contemp Clin Trials 2021

COcoa Supplement and Multivitamin Outcomes Study (COSMOS)

N=21,442
12,673 women aged ≥65 y and 8,769 men aged ≥60 y who are free of CVD and recently diagnosed cancer

- **Cocoa flavanols (600 mg/d)**
  - **Multivitamin**
  - **Placebo**
- **Placebo**
  - **Multivitamin**
  - **Placebo**

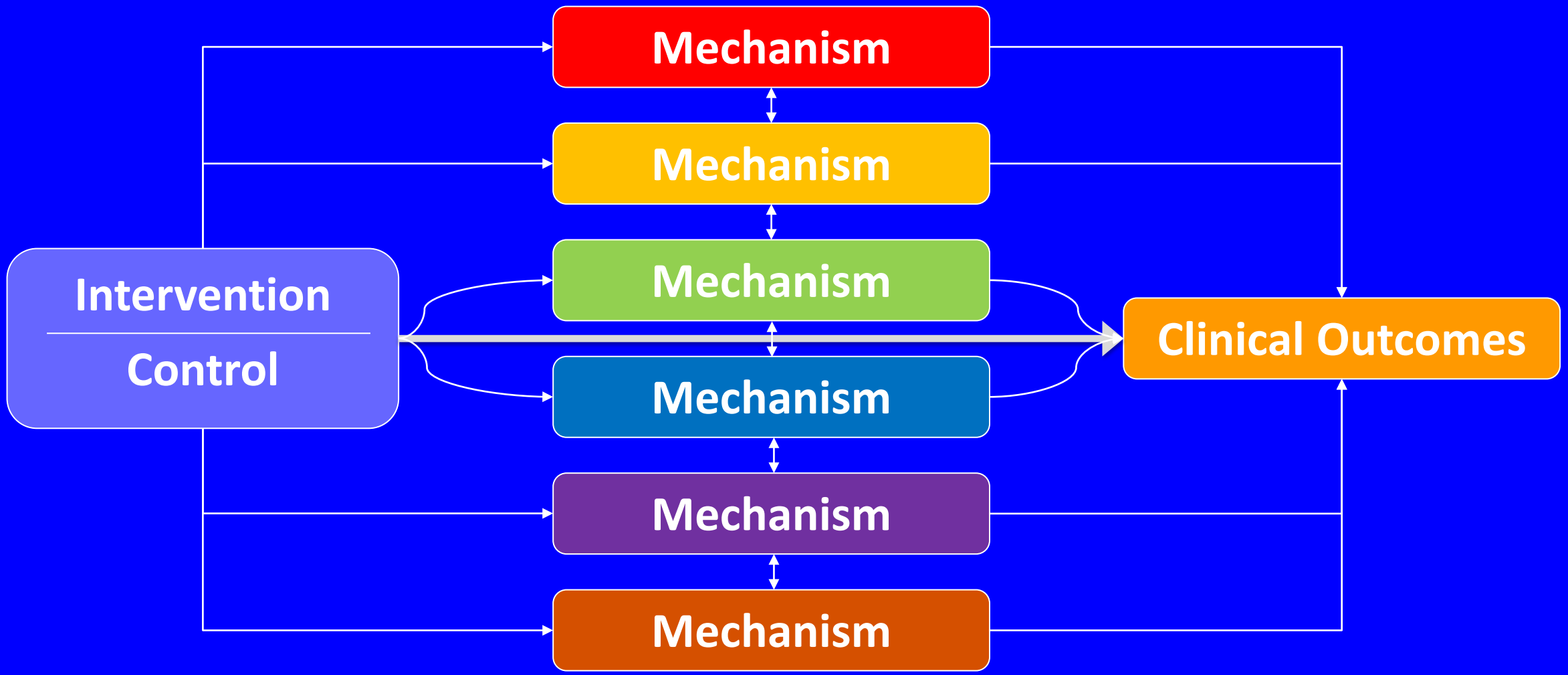
Median follow-up = 42.2 months

Primary Outcomes: Major cardiovascular events (MI, stroke, CVD death, coronary revascularization, angina, carotid artery disease, and peripheral artery disease) and total cancer (excluding non-melanoma skin cancer)

Baseline Blood/Urine Collection: 6,867 participants; follow-up collection in subset of participants at 1, 2, and 3 y

Baseline Clinic Visit: 603 Boston-based participants; follow-up clinic visit in 535 participants at 2 y

Hybrid Clinical Trial

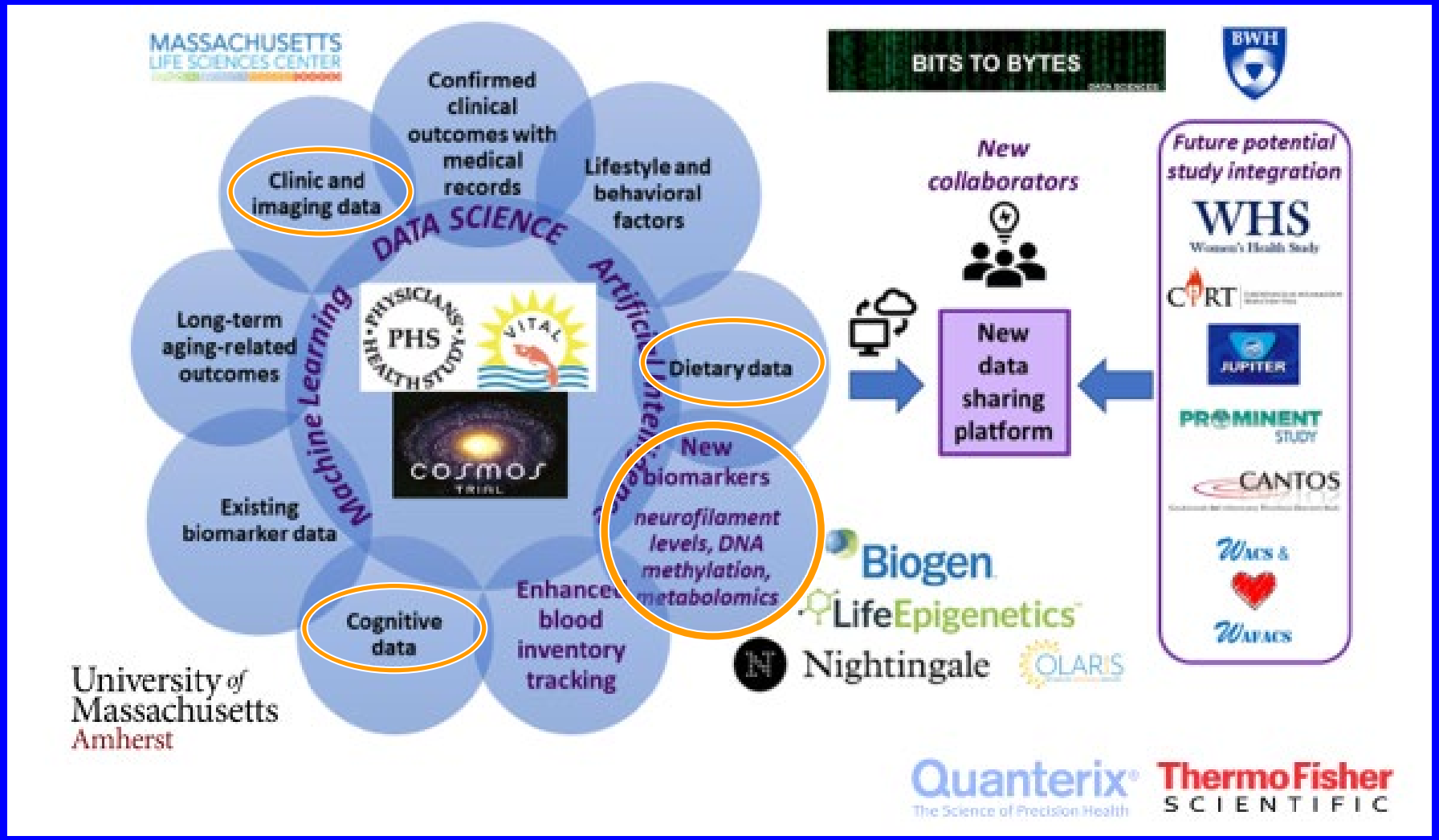


COSMOS Ancillary Studies: Brain Health

Daily MVM includes 250 µg lutein and 1000 IU vitamin D

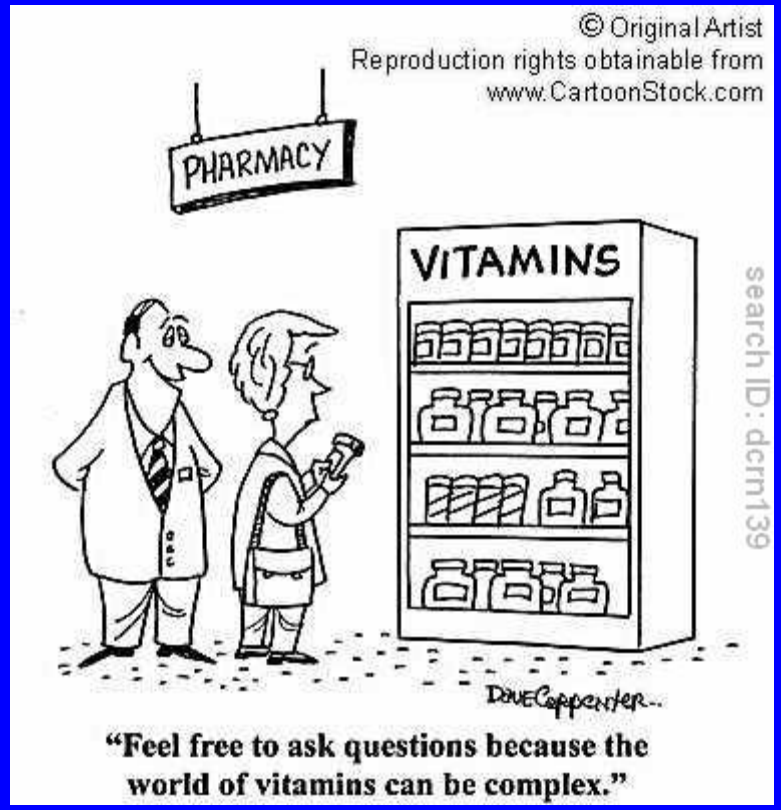
	COSMOS Blood	COSMOS Clinic	COSMOS Web	COSMOS Mind
Lead/Support	BWH/MSS	BWH/MSS	Columbia/MSS	Wake Forest/NIH
Assessments	***Blood, urine,*** *blood pressure (BP), body mass index (BMI), waist-to-hip ratio (WHR)*	***Blood, urine****, fecal samples, BP, 24h ABP, BMI, WHR, pulse wave velocity,* ***cognitive and physical function****, DXA,* ***MRI***	***Web-based cognitive assessments*** *(ModRey, ModBent, Flanker Test, Spatial Memory Test)*	***Telephone-based cognitive assessments*** *(TICSm, Immediate & delayed story recall, Oral trail making test, Verbal fluency)*
Baseline	**6,867**	**603**	**3,958**	**2,262**
Year 1	**2,155**	**-**	**3,327 (84%)**	**2,035 (90%)**
Year 2	**2,005**	**535 (89%)**	**3,058 (77%)**	**1,909 (84%)**
Year 3	**1,283**	**-**	**2,909 (73%)**	**1,789 (79%)**

Neurofilaments and neurodegenerative outcomes: Exploring the role of diet through data science



Conclusions

- There are important considerations when interpreting clinical trials of nutrients on cognition and mental well-being
  - Role of baseline nutritional status
    - Diet
    - Biomarkers
  - Identification of viable mechanisms of effect
    - Combine clinical outcomes with promising mechanistic pathways
  - Clinical trial design
    - Quality matters!
    - Small- and large-scale trials must complement each other
    - A good trial answers your questions – plus generates *new questions* to be answered in subsequent trials



"Feel free to ask questions because the world of vitamins can be complex."