Multivitamins for Life(span): What does everyone know that they are not telling me?

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Department of Veteran Affairs National Institutes of Health State of New York Indian Trail Foundation

Supplements:

Daily: Vitamin D Kinda daily: Nicotinamide riboside (~B3) Sporadically: Zinc, B12, K2, Melatonin Rarely: Multivitamin

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The Mystery of Successful Aging



Healthspan



Phys Ed

By GRETCHEN REYNOLDS JULY 12, 2017

https://nyti.ms/2u7BdB3

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Seldeen et al. J Gerontol 2017

High intensity interval training program for mice



Session Time: Frequency: 10 minutes 3 times a week



Speeds increase every two weeks Intensity customized to the mouse

Seldeen et al. J Gerontol 2017

HIIT Boosts Healthspan *** *** ** ** Grip Treadmill

Strength

Treadmill Endurance

Uphill Sprint Gait Endurance Speed

Seldeen et al. J Gerontol 2017

To The Bedside

YORK

THE BUFFALO NEWS

NEW

REFRESH

HEALTH + FITNESS + NUTRITION + FAMILY

WESTERN

te a few days a week can have benefits." - Kenneth Seldeen, research assistant professo e a jew aays a week can nave venegus. - Kennein Seueen, research assistant projesso riatric medicine in the University at Buffalo Jacobs School of Medicine & Biomedical

SATURDAY, NOVEMBER 30, 2019

INTENSITY **BOOSTS FITNESS**

Older WNY veterans lead the way in showing its effectiveness. Page 8

the the strength of his grip. Above, Nikhil Photos by Robert Kirkham/Buffalo News we calls earlier this month at the Veterans Medical ney Avenue.

maximum oxyge measured during on a treadmill at "All of these at to functional cap nity," Troen said. Veterans conti the company of the conti the same battery visit, with an eye results change. Veterans are to minutes while rid bike three times : by pedaling for 3 maximum oxyger by I minute at 80 at 50% three time another minute-k the end. This involves a of high-intensity "I think they t times, but I felt in the 85-year-old M complained a litt/ felt awoke, wantij exercise." He wasn't alor and Bill Pichcusk they participated Minor, 66, wh Belt neighborhoc Marine Corps fre The retired Gene truck driver - wi exercise-type per diabetes and is a survivor. He no l carrying grocerie to his second-floc getting out of his ing TV to do squ start fitness trait Pichcuskie, 62 is a former Marin who spent 20 year the Reserves. He a stent in a coron tension and rheur Nonetheless, he r cross-country ski wife, Nancy, who told him about th "I did it to see Pichcuskie said. myself and really I could. I felt grea He boosted hi

See Study on Page

To The Bedside

Pilot study to examine recruitment and administration of HIIT in older Veterans



HIIT is well tolerated and viewed favorably



Physical Activity and Enjoyment Scale (PACES) Survey

HIIT increases strength



HIIT increases endurance



HIIT increases overall quality of life



But... who likes exercise?

Achieved exercise guidelines: Age 65-74 15.3% Age 75+ 8.7%

CDC 2016



Boosting NAD+ to enhance performance



Nicotinamide Riboside (NR) can replenish NAD!



Does NR Work?



NR increases muscle NAD+



NR increases endurance



Is this for real?



NR increases endurance, again!



NR Improves Gait Speed



NR-VETs Trial

Study to examine efficacy of NR supplementation in older Veterans for functional capacity

Participants:

N = 144: 72 male and 72 female Age: 65-85 years Any race Non-frail / pre-frail VETERANS (or spouses) ClinicalTrials.gov/show/ NCT04691986

Starting April 2021

For more information please contact: Seldeen@buffalo.edu



1. Heaney RP. Am J Clin Nutr. 2004;80(suppl):1706S-1709S.

2. Thomas MK et al. N Engl J Med. 1998;338:777-783.

Vitamin D Insufficiency "The stealthy epidemic"



~ 50% below < 30 ng/ml¹

> 70% estimated to be
< 30 ng/ml nationally²



Zhang et al. Clinica Chimica Acta 2015
 Wei et al. Mol Nutr Food Res 2010
 Cherniack et al. J Am Geriatr Soc 2011

Low vitamin D supplementation establishes chronic insufficiency



→1000IU →125IU →125IU →1000IU



Seldeen et al. unpublished

Chronically vitamin D insufficient mice exhibit shorter stride length



Seldeen et al. unpublished

✓ Vitamin D → COVID-19 severity in VA patients

| | | COVID-19 Negative | COVID-19 Positive | |
|----------|-------|-------------------|-------------------|--|
| | | (N=51,492) | (N=4,549) | |
| 25(OH) D | < 20 | 8,757 / 17% | 876 / 19% | |
| ng/ml | 20-29 | 14,018 / 27% | 1,266 / 28% | |
| | ≥ 30 | 28,717 / 56% | 2,407 / 53% | |

- > $25(OH)D < 20 \& 20-29 \implies \textbf{hospitalization}$
- > 25(OH)D < 20 ➡ **↑ICU**
- > 25(OH)D < 20 \rightarrow **†** mortality

No sig association with pneumonia/ARDS

Seldeen, Troen, et al. 2020 (unpublished data)

Individual vitamins may do good things... but what about...



Multivitamins: Should you take them or not?



MOST STUDIES, and there have been many, say that there's not really a benefit to taking those multivitamins, no matter what your age is. "There is limited evidence that [multivitamins] offer any significant health benefits," sold a September 2018 article in Harvard Health Publishing. Harvard Medical School and Johns Hopkins researchers point

things like global trends versus a medical doctor's treating individuals.)

"When you look at most studies, the answer as to whether a multivitamin reduces cardiovascular and cancer risk, is 'no," says Seldeen. "There are not many benefits for healthy individuals, and a lot of people find that surprising."

Statistics show that fifty percent of

every day is the place to get your vitamins and minerals. "If you have a balanced diet, you're probably getting everything you need from the foods you eat. People should look at what the best diet for them is as they age," he notes. "There are a lot of opinions about what's a 'healthy' or 'the healthiest' diet, but one common thread through every diet is a high intake

Jana Eisenberg

Multivitamins are widely popular

Approximately 50% of US adult population use supplements (NHANES III)

Gahche et al (2011) NCHS Data Brief, PMID: 21592424

- 64% of older adults use supplements Qato *et al* (2016) JAMA Intern Med, PMID: 26998708
- 83% of rural older adults use supplements Shade *et al* (2019) J Clin Nurs, PMID: 30589152
- Supplement industry has sales of over \$30 Billion in the US and \$100 Billion globally Hannon *et al* (2020) Nutr Diabetes, PMID: 32341338
- Most common reasons, "Improve or maintain" Bailey et al (2013) JAMA Intern Med, PMID: 23381623

The History of Multivitamins



1897 Christiaan Eijkman

 Made keen observation that brown rice prevents beri-beri





1898 Sir Frederick Hopkins

 Postulated the existence of "accessory factors"

1912

Kazimierz Funk, at age 26

- Isolated substance that prevents Beri-beri
- Coined phrase Vitamine
- Published an article proposing the presence of 4 vitamines
 - Beri-beri
 - Scurvy
 - Pellagra
 - Rickets

1920's



"The claims set forth on the labels of the medicinal values of these preparations are extravagant and misleading"

-Journal of the American Medical Association, 1922



World War II



- In recruitment of service for WWII it was found that one third suffered from malnutrition
- In response, President Franklin D. Roosevelt establishes the first set of recommended daily allowances (RDA) in 1941
- The first "One-a-day" supplement appears in 1943

Establishing nutritional requirments





Recommended Daily Allowances (RDA) a.k.a. dietary reference intakes (DRI)

1941: Vitamins A, B1, B2, B3, C, and D, calcium, and iron.

1968: Vitamins E, B6, and B12, and magnesium join the list

Today: Vitamins A, B1 (thiamin), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6 (pyridoxine,) B7 (biotin), B9 (folic acid), B12 (cobalamin), C, D, E, K, choline, calcium, chromium, copper, iodine, iron, magnesium, manganese, molybdenum, phosphorus, selenium, zinc, potassium, and chloride.

The National Academy of Medicine



- Review current literature
- Set "recommended dietary allowances (RDA)" of various nutrients broken down by age and sex
- Set "Adequate intake (AI)" for nutrients that have insufficient literature
- Set "Tolerable Upper Intake Limits (UL)" for maximal levels unlikely to cause adverse health effects

https://ods.od.nih.gov/HealthInformation/Dietary_Reference_Intakes.aspx

2021: How does one choose?

289-306 of over 8,000 results for "multivitamins"



Cost per day of 25 randomly selected multivitamins:

| | Low | Mean | Median | High |
|------|--------|--------|--------|--------|
| Cost | \$0.03 | \$0.42 | \$0.40 | \$0.93 |

"No statistically significant difference was found on the basis of cost" Jones et al (2021) J AM PHARM Assoc, PMID: 33414014

Many MVs push the limits!

| % | Low | Mean | Mode | Median | High |
|------------------|-----|------|------|--------|-------|
| Vitamin A | 12 | 233 | 117 | 167 | 1,250 |
| Vitamin C | 20 | 226 | 67 | 67 | 1,111 |
| Vitamin D | 0 | 166 | 50 | 50 | 2,240 |
| Vitamin E | 38 | 229 | 90 | 133 | 1,000 |
| Vitamin K | 21 | 52 | 21 | 32 | 100 |
| Thiamin | 50 | 717 | 125 | 125 | 4,167 |
| Riboflavin | 46 | 641 | 131 | 131 | 3,846 |
| Niacin | 50 | 156 | 125 | 125 | 625 |
| Viatmin B6 | 41 | 454 | 118 | 118 | 2,941 |
| Folate | 25 | 108 | 100 | 100 | 168 |
| Vitamin B12 | 50 | 1178 | 250 | 292 | 8,333 |
| Biotin | 33 | 359 | 100 | 200 | 1,000 |
| Pantothenic Acid | 52 | 352 | 200 | 200 | 1,600 |
| Calcium | 1 | 14 | 15 | 14 | 25 |
| Iron | 11 | 68 | 100 | 89 | 100 |
| Phosphorus | 2 | 6 | #N/A | 7 | 9 |
| lodine | 15 | 74 | 100 | 100 | 100 |
| Magnesium | 0 | 20 | 24 | 24 | 71 |
| Zinc | 3 | 83 | 136 | 100 | 136 |
| Selenium | 2 | 87 | 100 | 100 | 287 |
| Copper | 2 | 91 | 56 | 78 | 222 |
| Manganese | 1 | 112 | 100 | 100 | 304 |
| Chromium | 5 | 148 | 100 | 100 | 343 |
| Chloride | 3 | 3 | 3 | 3 | 3 |
| Potassium | 0 | 1 | 2 | 1 | 5 |
| Molybdenum | 22 | 115 | 100 | 100 | 333 |
| Choline | 0 | 2 | 5 | 1 | 5 |

And what else do you get? Aloe Vera Gel, Alpha Lipoic Acid, Amylase, Apple Pectin, Bee Pollen, Betaine, Boron, Brewer's Yeast, Bromolean, Chlorine Bitartrate, Chlorophyll, Citrus Bioflavinoids, Co-enzyme Q-10, Colloidal Minerals, Cysteine, Echnicea, Eluthero, Ginseng, Glycine, Gotu Kola, Green tea, Hesperidin, Inositol, Kelp, Lacobacillus A., L-Arginine, Lecithin, Lipase, Lutein, Lycopene, Lysine, Methionine, Oat Extract, Octacosoanol, **Omega 3/6/9 Seed Blends, PABA, Papain, Peat** extract, Proprietary Blends, Psyllium, Quercetin, RNA, Rutin, Safflower, Silicon, Sodium, Spirulina, Superoxide Dismutase, Vanadium, Vitamin K2, Wheat Grass Powder

Publication interest in Multivitamins

"Vitamin D" **88,465**

"Vitamin B" 41,210 "Vitamin A" **36,020**

"Vitamin K" 28,023 "Vitamin C" 24,485

"Multivitamin" 4035

MVs and All Cause Mortality

Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX)

Hercberg *et al* (2004) Arch Internal Med, PMID: 15557412 5 component multivitamin – 13,017 participants (aged 35-60 at start) Double blind/placebo controlled trial

7.5 year follow-up

Trend towards reduced all-cause mortality in men but not women

Physicians Health Study II

Sesso *et al* (2012) JAMA, PMID: 23117775 30 component multivitamin – 14,641 Male physicians 50 and older Double blind/placebo controlled trial

~11.2 year follow-up

No significant reduction in all cause mortality

Linxian general population nutrition intervention trial

Wang *et al* (2013) JAMA, PMID: 23712839 5 component multivitamin – 3,318; 40-69 diagnosed with esophageal dysplasia Double blind/placebo controlled trial 6 year supplementation and 20 years post-supplement follow-up **No significant reduction in all cause mortality**

MVs and All Cause Mortality

EPIC-Heidelberg: Prospective study

Li *et al* (2012) Eur J Nutr., PMID: 21779961 Multivitamins or antioxidants – 23,943 Database mining ~11 year follow-up

No significant reduction in all cause mortality across all participants But – baseline antioxidant users had a significant reduction! "the sick user effect"

UK Biobank: Prospective study

Behrendt *et al* (2020) Antioxidants, PMID: 33339307 Multivitamins or antioxidants – 345,626 baseline age ~57 years Database mining ~11.5 year follow-up

No significant reduction in all cause mortality

MVs and cardiovascular disease

Physicians Health Study II

Sesso *et al* (2012) JAMA, PMID: 23117775 30 component multivitamin – 14,641 Male physicians 50 and older Double blind/placebo controlled trial ~11.2 year follow-up

No significant reduction in all cause mortality

Trial to Assess Chelation Therapy (TACT)

Lamas *et al* (2013) Antioxidants, PMID: 24490264 28 component multivitamins – 1,708; age 50+ years; post-MI population Double blind/placebo controlled trial

~4.6 year follow-up

Did not reduce cardiovascular events

MVs and cardiovascular disease

Trial to Assess Chelation Therapy (TACT)

Issa *et al* (2018) Antioxidants, PMID: 29224648 28 component multivitamins – 1,708; <u>no-statins</u> Double blind/placebo controlled trial ~4.6 year follow-up

"Seem" to decrease combined cardiac events

- → TACT2 upcoming
- → However criticisms include co-investigators disciplined by state medical boards & high dropout rates, misrepresentation on informed consent (Maron 24952853)

Systematic Review: Multivitamins for CVD prevention

Kim *et al* (2018) Circ Cardio Qual Outcomes, PMID: 29991644 18 studies; ~2,019,862 participants across all studies **"MVM supplementation does not improve CVD outcomes in the** general population"

MVs and Cancer

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7.5 year follow-up

Lowered total cancer incidence in men but not women

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No significant reduction in cancer

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No significant reduction in cancer

MVs and Cancer

Dietary supplement use after cancer diagnosis

Kanellopoulou et al (2020) Nutr Cancer, PMID: 32148118

Review - Multivitamins

"mostly based on observational studies"

Lowered cancer recurrence, but, "More RCTs needed to justify recommendation for use

Are we getting our vitamins naturally?

"HEALTHY" DAY

Breakfast: Honey nut cheerios, Whole milk, orange juice
Lunch: McDonald's Caesar salad, fries, trail mix
Dinner: Chicken breast, salad (romaine, tomato, celery, mushroom, Italian dressing), mashed potatoes, asparagus

"SUPER HEALTHY" DAY

Breakfast: Smoothie (kale, walnut, strawberries, apple, mint, coconut water)
Lunch: Portabella salad (romaine, arugula, quinoa, portabella mushroom, heirloom tomatoes, celery, vinaigrette, 2 hard boiled eggs)
Dinner: Wild Atlantic salmon, bulgur
Dessert: Chocolate soft serve (frozen banana, cocoa powder, maple syrup, whole milk, pecans)

"FUN" DAY

Breakfast: Pancakes (butter syrup), hash browns, bacon
Snack: Caramel Frappuccino
Lunch: BK Whopper, Large Fry, Oreo Milkshake
Dinner: T-bone steak, mashed potatoes, wine
Dessert: Cherry pie

Are we getting our vitamins naturally?

% of RDA

Vitamin A

Vitamin C

Vitamin D

Vitamin E

Vitamin K

Thiamin

Riboflavin

Niacin

Vitamin B6

Folate

Vitamin B12

Pantothenic acid

Phosphorus

Calcium

Iron

Magnesium

Zinc

Selenium

Copper

Manganese

Potassium

And... the human body is quite robust



Ryan Howarth has spent the last 17 years almost exclusively chomping on chicken nuagets Credit: Caters News Agency

Multivitamins are relatively safe, but...

Systematic Review: Safety

Biesalski *et al* (2012) Nutrition, PMID: 27553772 >9 component multivitamins –15 studies; >10 years follow-up **"Safe for long term use"** 2018 American Association of Poison Control Centers: 48,630 events 1697 minor adverse events 189 moderate 5 major <u>and no deaths</u>.

MVM addresses nutritional deficiencies, but may reach excess Wallace *et al* (2019) J Nutr Geron Geriatri, PMID: 31502930 Survey older adults >51 years of age Regular MVM use decreased odds of deficiency for several nutrients, but increased risk of exceeding tolerable intake of folic

Vitamins, Are they Safe?

acid

Hamishehkar *et al* (2016) Adv Pharm Bull, PMID: 28101454 Review on harmful and detrimental properties of vitamins "Our recommendation is that taking high-dose supplements of vitamins A, E, D, C, and folic acid is not always effective for prevention of disease, and it can even be harmful to the health."

Polypharmacy and Drug interactions

Aloe Vera Gel, Alpha Lipoic Acid, Amylase, Apple Pectin, Bee Pollen, Betaine, Boron, Brewer's Yeast, Bromolean, Chlorine Bitartrate, Chlorophyll, Citrus Bioflavinoids, Co-enzyme Q-10, Colloidal Minerals, Cysteine, Echnicea, Eluthero, Ginseng, Glycine, Gotu Kola, Green tea, Hesperidin, Inositol, Kelp, Lacobacillus A., L-Arginine, Lecithin, Lipase, Lutein, Lycopene, Lysine, Methionine, Oat Extract, Octacosoanol, **Omega 3/6/9 Seed Blends, PABA, Papain, Peat** extract, Proprietary Blends, Psyllium, Quercetin, RNA, Rutin, Safflower, Silicon, Sodium, Spirulina, Superoxide Dismutase, Vanadium, Vitamin K2, Wheat Grass Powder

Polypharmacy and drug interactions

Changes in Prescription and supplement use 2005 v 2011

Qato *et al* (2016) Nutrition, PMID: 26998708 In-home interviews of community dwelling adults aged 62-85 "In 2010-2011, approximately 15.1% of older adults were at risk for a potential major drug-drug interaction compared with an estimated 8.4% in 2005-2006 (P < .001). Most of these interacting regimens involved medications and dietary supplements"

Prevalence of polypharmacy in border dwellers

Loya *et al* (2009) Nutrition, PMID: 19552494 Surveys of 130 participants (~71.4 years) living near the US-Mexico border

- Polypharmacy prevalence: 72.3%
- Major polypharmacy: 38.5%
- > Polyherbacy: 26.2%

Estimated 31.5% at risk for drug-supplement interaction

Discussion

- Multis are relatively safe and inexpensive but do not appear to confer significant long-term health benefits
- Multis may be good at reducing malnutrition in older adults
- Overall, the literature is underwhelming particularly on the topic of polypharmacy and drug interactions
- Never doubt the power of placebo! "MVM users self-reported better overall health despite no apparent differences in clinically measurable health outcomes." Paranjpe *et al* (2020) BMJ Open, PMID: 33148746

Choosing a multivitamin

- See a dietician / nutritionist
- Evaluate your current nutritional intake:





- Avoid high dose multivitamins (or don't take daily)
- Use simpler multivitamins
- Vitamin D!



QUESTIONS?

Contact: seldeen@buffalo.edu