THE PATH AHEAD

Vitamin D (Like Every Nutrient) is a Team Player

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Abstract

Vitamin D is critical for many physiological functions in humans. Numerous population-wide assessments have shown that vitamin D deficiency is very common. Unfortunately, far too many studies intending to assess the clinical efficacy of supplementation are poorly designed. They look at vitamin D as an isolated agent, independent of the complex matrix required for it to be physiologically effective and at dosages inadequate for much of the population. These errors cause inappropriate and invalid results that are then misused to not only recommend against supplementation but to also recommend against even measuring vitamin D levels. This editorial addresses the weaknesses of typical vitamin D research, such as VITAL, and the key factors that must be addressed for accurate vitamin D research.

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Introduction

The latest anti-nutrient diatribe, published July 28, 2022, in *NEJM*, serves as yet another example of the failure of the drug paradigm to accurately evaluate the efficacy of a nutrient. In research based on the drug model, a single agent is expected to perform as a magic bullet to control/suppress disease symptoms. In this latest supposed analysis of vitamin D efficacy, what we have is even more absurd: the expectation that a single nutrient will act as a magic bullet to, by itself, prevent disease. This is not how human physiology works. A single nutrient intervention will only work if it is deficient, and if the other nutrients needed for it to function are adequate.

Well established physiology research has clearly shown, especially in relation to bone health, that vitamin D is a team player that works with calcium, magnesium, vitamin K2, vitamin A, vitamin C, and at least 12 trace minerals, such as boron. All are required for optimal bone renewal/fracture prevention. The interactive roles played by these nutrients in promoting bone health are fully discussed in our consumer book, *Healthy Bones, Healthy You!*[1]

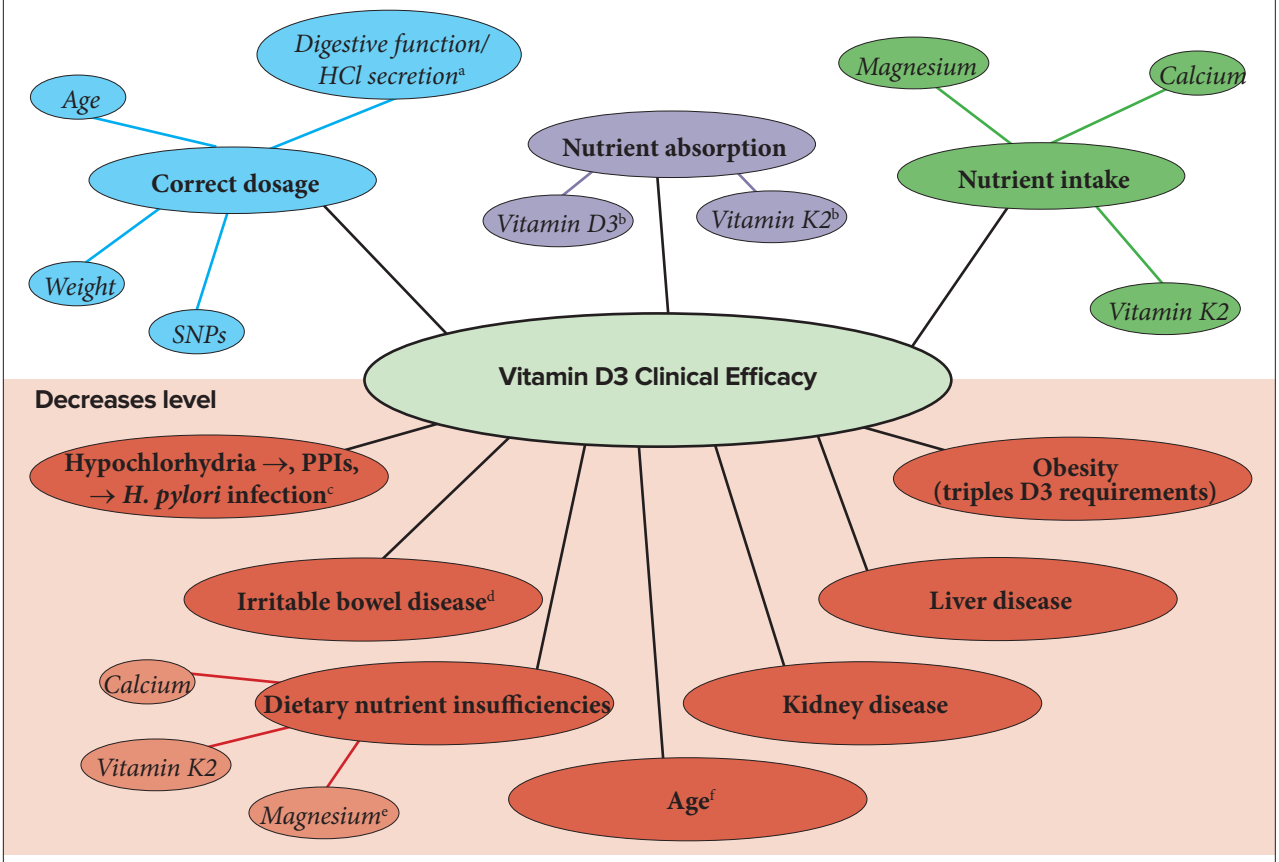
The assertions from the VITAL study and its ancillary reports that vitamin D supplementation is ineffective for essentially any health problem are invalid and will cause increased disease and suffering. This editorial addresses some of the problems with single nutrient research. Research that ignores the full matrix needed for a nutrient to work by not addressing common nutrient deficiencies and common health problems that impair a nutrient's function are unconvincing. We use here the example of many factors that greatly impact vitamin D's role in supporting bone remodeling. The same concerns raised in this editorial about vitamin D research are applicable to all nutrient research.

VITAL

The VITamin D and OmegA-3 TriaL (VITAL) investigated whether taking daily dietary supplements of vitamin D3 (2000 IU) or omega-3 fatty acids (1 g) reduces the risk of developing cancer, heart disease, and stroke in people who do not have a prior history of these illnesses. The design was a 2-by-2 factorial randomized clinical trial in 25 871 US men (50 years of age or older) and women (55 years of age or older). The participants were randomly assigned to 1 of 4 groups: vitamin D3 (cholecalciferol, 2000 IU per day) plus n–3 fatty acids (1 g per day), vitamin D3 plus placebo, n–3 fatty acids plus placebo, or double placebo.[3]

This latest report is an ancillary extraction of the results to look at fracture risk.[2] The authors assert that vitamin supplements do not have important health benefits in the general population of older adults, even in

Figure 1. Vitamin D Flowchart



[a]Atrophic gastritis affects 1 in 3 older adults in the U.S.[4]
[b]both D3 and K2 are fat-soluble, must be micellized for absorption, which requires bile, so absorption lowered if irritable bowel disease or gallbladder problems
[c]*H. pylori* infection present in 40-60% of elders with no gastrointestinal symptoms and in 70% of elders with chronic gastrointestinal complaints[5]
[d]ability to reabsorb bile impaired, increasing risk of fat-soluble vitamin deficiency as well as omega-3 deficiency[6-9]
[e]cofactor for 1α-hydroxylase, the kidney enzyme that converts 25(OH)D to 1,25-D
[f]age-associated decline in kidney function results in increased dosage requirement

those with low 25-hydroxyvitamin D levels. Unfortunately, the accompanying editorial furthers the misunderstanding of vitamin D and misrepresentation of nutrition research.[10]

The randomization looked good—for the parameters the researchers thought important. Unfortunately, they missed many key factors (discussed below) that assuredly swamped the effect they were testing.

Baseline blood samples were obtained from nearly 17 000 participants. Annual questionnaires collected information about numerous health outcomes. Results of analyses from VITAL previously published in peer-reviewed journals have shown that vitamin D supplementation did not prevent cancer or cardiovascular disease, prevent falls, improve cognitive function, reduce atrial fibrillation, change body composition, reduce migraine frequency, improve stroke outcomes, decrease age-related macular degeneration, or reduce knee pain.

In this ancillary study, LeBoff and colleagues added to the above negative findings that, contrary to expectations, vitamin D3 did not reduce the risk of fractures over a median follow-up of 5.3 years, even in the 20% of the participants taking supplemental calcium at a dose of up to 1200 mg per day.[3]

The long-anticipated results of VITAL are asserted to clearly demonstrate that daily supplementation with 2000 IU of vitamin D3 does not significantly reduce the risk of total, hip, or nonvertebral fractures. Subgroup analyses showed a similar lack of effect on fracture risk according to sex, age, race or ethnic group, body-mass index, and other characteristics.

The conventional medicine and consumer media are widely trumpeting this proves that supplemental vitamin D is ineffective, and this has led to recommendations to no longer support testing for vitamin D in addition to

recommending against supplementation. Unfortunately, the only valid finding from this study is that supplementing single nutrients is not effective. Which is what anyone who knows anything about nutrition and human physiology already knows.

Vitamin D Network Nutrients

Nutrients work as integral parts of complex metabolic networks. If parts of the network are not functioning properly, providing a single nutrient that does not address the components of the network that are dysfunctional will not have a beneficial effect. Unfortunately, many of the nutrients required for bone health are deficient in most of the population.

While numerous nutrients play vital roles in healthy bone renewal—in relation to vitamin D's efficacy in fracture prevention—3 of the most important are calcium, vitamin K2 and magnesium, all of which are consumed in less than RDI amounts by at least half the US population.

Calcium

Vitamin D is not going to do much if calcium intake—diet plus supplements—is grossly deficient. Some study subjects in the ancillary study of the Vitamin D and Omega-3 Trial (VITAL) received 1200 mg of supplemental calcium daily along with 2000 IU of D3. Many others did not. "A substantial proportion of people in the United States consume less than recommended amounts of calcium. An analysis of 2007–2010 data from the National Health and Nutrition Examination Survey (NHANES) found that 49% of children aged 4–18 years and 39% of all individuals aged 4 and older consume less than the EAR for calcium from foods and supplements."[11] Of particular concern is that the EAR (estimated average requirement) is the amount thought to meet the needs of just 50% of the population. If calcium is not present in the small intestine, vitamin D cannot enable its absorption.

Women aged 40-59 are supposed to be getting 1200 – 1500 mg/d of calcium, but their average dietary intake is only 882 mg/d—just a little more than half the amount of calcium women need to maintain a healthy skeleton, especially as they go through perimenopause and menopause. Average dietary calcium intake in women aged 60 and older is even lower at 842 mg/d.[12]

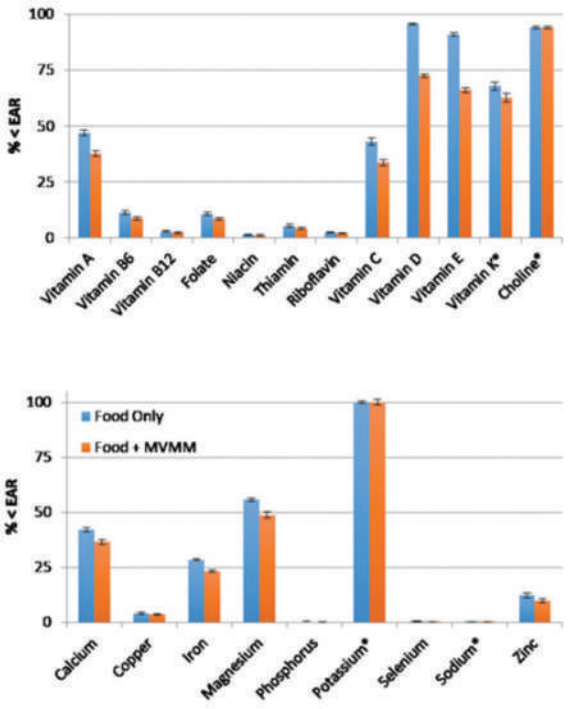
Furthermore, by age 65, calcium absorption is only 50% of adolescent absorption efficiency, in men as well as women. Men's version of menopause, andropause, also begins in their 50s and is accompanied by the same drops in calcium's intestinal absorption and reabsorption from the kidneys as seen in women. In elders, supplementation is increasingly important to ensure at least 1200 mg/d is provided from diet and supplements combined.[13-15]

Vitamin K2

While vitamin D is required for calcium's active absorption, which accounts for 85% of the calcium humans absorb, vitamin D does nothing to regulate what happens to the calcium whose absorption it enables. That requires vitamin K2, the cofactor for two Gla proteins: osteocalcin, which brings calcium into bone, and matrix Gla protein, which prevents calcium from depositing in soft tissues, such as the cardiovascular system and kidneys. K2 is found in high amounts in a Japanese fermented soybean product called natto but is infrequently seen in the Western diet, although very small amounts are present in certain full fat cheeses and pasture-raised eggs.[16-19]

Vitamin K2 insufficiency is very common in US adults. A recent study that measured circulating undercarboxylated MGP levels (a more accurate method than measuring prothrombin time since K2 is primarily used to activate the Gla proteins), found K2 deficiency or insufficiency in 97% of older subjects in a mixed population.[20]

Figure 2. Prevalence of Nutrient Deficiencies in US Adults



Magnesium

Magnesium insufficiency is also all too common and impairs vitamin D's activation. Magnesium is the cofactor for 1α-hydroxylase, the renal enzyme that converts 25(OH) D to $1,25(OH)_2D$. As the following table shows, approximately 48% to 55% of the US population consumes less than the EAR for magnesium. Obviously, if vitamin D is not converted to its active hormonal form, it will not beneficially affect physiology.[21]

Nutrient insufficiencies are very common in U.S. Figure 2 shows the percentages not meeting the EAR (which, by definition, means that only 50% of the population would be able to survive on that level of a

nutrient before experiencing ill effects from inadequate nutrition). The high percentages of people not even meeting the poor EAR standard is very worrisome.[21]

Metabolic Issues Impairing Vitamin D Function

Maldigestion

Also required for fracture prevention is effective digestion, without which calcium and D3 are poorly absorbed. Another requirement is well-functioning liver and kidneys, without which D3 will not be activated—first to 25(OH)D and then finally to its active hormonal form of $1,25(OH)_2D$.

Effective digestion depends upon the presence of stomach acid, whose secretion is prevented by the use of proton pump inhibitors. "Proton pump inhibitors (PPIs) are among the most commonly used drugs in the world. About 15 million people in the U.S. use PPIs every year… For those who take PPI drugs long-term, side effects can be serious or even deadly. Proton pump inhibitor side effects include kidney problems, bone fractures and heart attacks… Thousands of people have filed PPI lawsuits. They claim PPIs caused kidney failure and other injuries."[22]

This is not just a problem in the United States. In 2016 in Australia, the prevalence and incidence of PPI use was 12.5 and 3.9 per 100 people, respectively. Furthermore, prevalence and incidence were highest among people 65 years and older, particularly older women.[23] Similar results have been shown in other countries. In Iceland between 2003 and 2015, annual prevalence increased from 8.5 per 100 persons to 15.5 per 100 persons, increased with patient age, and was higher among women.[24]

Liver Dysfunction

Liver disease is rampant in the United States, as can be seen in Table 1. As would be expected, people with severe liver disease have lower levels of vitamin D, but more importantly are less able to convert dietary vitamin D3 to 25(OH)D, the still inactive form in which vitamin D circulates in the bloodstream. This helps explain why patients with NAFLD have a higher prevalence of osteopenia and osteoporosis.[25,26]

Table 1. Nonalcoholic Fatty Liver Disease[27]

USA NAFLD	30%
USA Nonalcoholic steatohepatitis	5%
Global NAFLD	25%

Kidney Dysfunction

Unfortunately, kidney failure is another chronic disease that is increasing relentlessly worldwide and is now common in the United States, as shown in Table 2. As would be expected, as kidney function decreases, so does its ability to perform the second hydroxylation needed to create the active version of vitamin D: $1,25(OH)_2D_3$. The glomerular filtration rate of a healthy 20-year-old man is about 140 mL/min. The glomerular filtration rate of a healthy 70-year-old man is about 90 mL/min. This age-typical decline in kidney filtration function increases the amount of 25(OH)D needed in the blood to sustain adequate production of 1,25-D by more than 50%. Current Institute of Medicine recommendations, even though they are still far too low to produce optimal health, recognize that people over age 70 may need 3 times more vitamin D than young adults.[28]

Table 2. Prevalence of Chronic Kidney Disease[29,30]

USA Adults	15%
USA Adults >65	38%
9 in 10 don't know they have kidney disease	
2 in 5 with severe disease don't know they have kidney disease	
Global	13.4%

Vitamin D Dosage

Obesity

In addition to failure to consider any of the above factors affecting vitamin D efficacy, the dosage of vitamin D3 used was 2000 IU per day. This dose is inadequate for anyone who is obese, most who are overweight, and many who are of normal weight, a large number of whom, including these authors, require 4000 – 6000 IU/d.

Individuals who are significantly overweight or obese require far more vitamin D than normal weight individuals. A high BMI doubles or even triples vitamin D needs. A review of 94 studies was conducted to determine how much supplemental vitamin D people of different body weights needed in order to bring their serum 25(OH)D levels into adequate range. A person weighing 110 pounds (50 kg) required 1680 IU/d of D3 to achieve a 25(OH)D level of 30 ng/mL. A person weighing 165 lbs (75 kg) required 2500 IU/d, and someone weighing 220 lbs (100 kg) needed 3360 IU/d.

A meta-analysis looking at the research identifying the prevalence of vitamin D deficiency in the obese identified 15 studies involving 3867 obese subjects and 9342 normal weight controls. Obese individuals who were European or American had a 370% increased risk of vitamin D deficiency. Obese Asian individuals had a 343% increased likelihood of being vitamin D deficient. In other words, regardless of the latitude where an individual lives, his or her age or nationality, if obese, that individual is almost certainly vitamin D deficient.[31,32]

The Endocrine Society's weight-based recommendations for supplemental vitamin D3 are that vitamin D supplementation should be 1.5 times higher for overweight subjects, and 2 to 3 times higher for obese subjects compared to normal weight subjects. Table 3 provides the specific body weight recommendations to achieve 25(OH)D targets. We believe optimal levels of 25(OH)D are 60-80 ng/mL.[33,34]

Figure 3. Prevalence of Obesity by State[35]

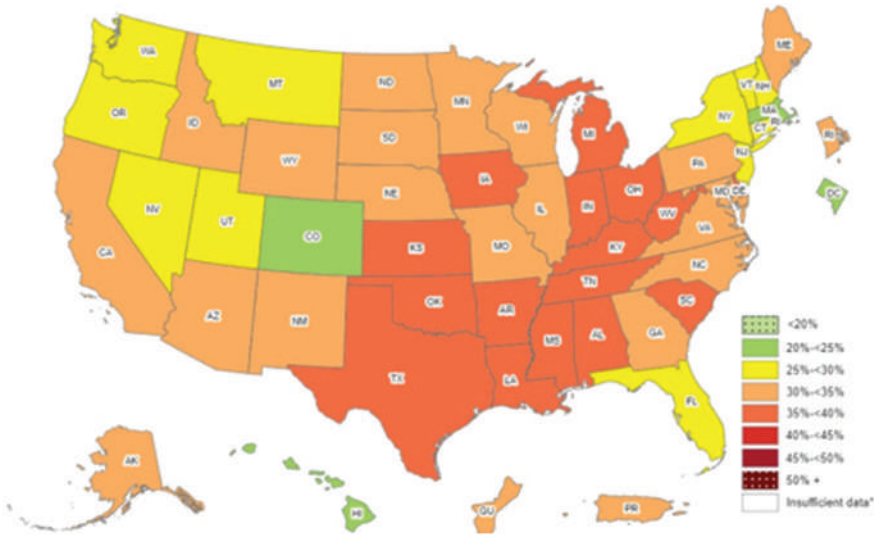


Table 3. Response to Vitamin D Supplementation Depends Upon BMI

Vitamin D Dose IU/d	Serum 25(PH)D Level ng/mL		
	Normal Weight	Overweight	Obese
1000	35.2	32	28
2000	39.6	36	31.2
4000	47.2	42.8	36.4
10 000	60.4	56	48.4
20 000	65.2	61.2	54

Lara requires approximately 6000 IU/d—even taking 2000 IU of this amount sublingually to bypass problems maintaining adequate vitamin D due to common hydroxylase enzyme SNPs she carries. (The hydroxylase enzymes both activate and catabolize vitamin D.) Other commonly found SNPs affecting vitamin D efficacy include at least 4 VDR variants, and SNPs in vitamin D binding protein. For individuals who are carriers of any of these SNPs, 2000 IU would not be adequate. A study of Iranian women with osteoporosis found that over half of them had one or more SNPs impairing vitamin D metabolism.[36]

The high prevalence of functional vitamin D deficiency is impactful far beyond bone health. For example, we have learned from the COVID-19 pandemic that susceptibility to infection and severe disease is inversely proportional to vitamin D levels.[37]

The optimal range for resistance to SARS-CoV-2 infection and severe COVID-19 disease has not been determined. However, we believe it is in the range of 60 - 80 ng/mL 25(OH)D, not 30 ng/mL.[38-40]

Age

A review of several studies found that adults aged 65 or older whose blood levels of vitamin D are less than 30 ng/mL need more supplementary vitamin D3 than young adults to improve their vitamin D status. If a younger adult needs 2000 IU/d, then those aged 65 or older would require 5000 IU/d to bring their 25(OH)D levels up into optimal range (60-80 ng/mL). One of the reasons for this increased requirement is age-associated decline in kidney function, as discussed above.[41]

Many Critical Factors Missed by VITAL

Hopefully, the above discussion makes clear that many factors hugely impacting vitamin D efficacy were missed. Table 3 lists these and others:

Table 4. Vitamin D Confounding Factors Not Controlled for in VITAL

- Calcium intake
- Magnesium intake/magnesium status
- Digestive function
- PPI use
- Undercarboxylated osteocalcin or matrix Gla protein (a marker of vitamin K2 status)
- Atrophic gastritis/*H. pylori infection*
- NAFLD
- CKD
- IBS

Our decisive verdict on this paper and on research using the single nutrient paradigm: an incredible waste of money and unfortunate source of misinformation.

Conclusion

What does this latest report from VITAL actually tell us? Providing vitamin D alone or omega-3s alone, or even a combination of D3 and omega-3s (both at dosages too low to produce significant beneficial effect as demonstrated by numerous other studies), is not helpful. For anyone whose medical school education included the interactions among micronutrients in human physiology, this is not a surprise, but is what would be expected.

Unfortunately, these highly questionable (at best) VITAL results are being used in ways that will impair population health. From Osteoporosis Canada[42]: "The screening of 25-hydroxyvitamin D levels in the general population is currently not recommended. However, there may be specific situations where vitamin D testing may be of clinical use. These include patients with co-morbidities which affect vitamin D absorption and metabolism, where testing may help identify significantly low 25-hydroxyvitamin D levels and facilitate correct dosing of vitamin D supplementation. These co-morbidities include malabsorptive disease, renal disease, living in institutionalized settings, and taking certain medications which may affect vitamin D metabolism. Screening lab tests may also be useful prior to the initiation of anti-resorptive agents for osteoporosis, as low 25-hydroxyvitamin D levels may be a risk factor for hypocalcemia." Note that almost all the issues we raised above were ignored.

If the intent is to discredit the clinical efficacy of a nutrient, test it like a drug. In general, drugs work by poisoning enzymes, while nutrients work as necessary enzyme cofactors, constituents of body tissues, etc. This is, of course, an oversimplification. Nonetheless, look at the most commonly prescribed drugs—9 of 10 are simply enzyme poisons. In contrast, the most commonly used nutrients are required cofactors for enzymes. The treatment of osteoporosis provides a great example of this dichotomy. Osteoporosis is caused by an imbalance between bone resorption and bone regrowth. The drug approach is to poison the enzymes used to reabsorb bone, a key process in bone remodeling. This results in apparent short-term benefit—maintaining bone density—but at the cost of long-term increased bone fragility since the old, damaged bone is not replaced. (Bone remodeling is coupled. Osteoclastic bone resorption releases a myriad of growth factors that were stored locally in the bone matrix. These growth factors then attract osteoblasts and their mesenchymal stem cell precursors to the remodeling site and stimulate their proliferation, differentiation, and activity. In effect, osteoclasts' resorption activity liberates a bone renewal savings account initially deposited by osteoblasts. No osteoclast activity. No osteoblast activity.[43]

In contrast, vitamin D—IN COLLABORATION WITH SEVERAL OTHER VITAMINS AND MINERALS—supports bone rebuilding. Osteoporosis is very rarely simply due to excessive bone resorption. The primary cause is a deficiency of the nutrients necessary for proper bone rebuilding. Not only does the drug approach result in suboptimal bone density, but the nutrient deficiencies—which of course the drugs do not address—continue unabated resulting in additional damage elsewhere in the body.

We suffer the highest burden of chronic disease in every age group ever in human history. Why? Because the drug model is mainly useful for acute disease. By not addressing the rampant nutrient deficiencies and ever-growing toxic burden, the world will continue to suffer ever increasing chronic disease.

References

1. Pizzorno L, Pizzorno J. Healthy Bones, Healthy You! ISBN 97-1-77779-250-3
2. https://www.cdc.gov/obesity/data/prevalence-maps.html accessed 8/2022
3. LeBoff MS, Chou SH, Ratliff KA, et al. Supplemental Vitamin D and Incident Fractures in Midlife and Older Adults. *N Engl J Med*. 2022;387(4):299-309. PMID:35939577 doi:10.1056/NEJMoa2202106
4. Russell RM. The aging process as a modifier of metabolism. *Review Am J Clin Nutr*. 2000 Aug;72(2 Suppl):529S-32S. PMID:9650019
5. Pilotto A, Franceschi M. Helicobacter pylori infection in older people. *World J Gastroenterol*. 2014 Jun7; 20(21):6364-6373. PMID:24914358
6. Oh HJ, Ryu KH, Park BJ, Yoon BH. Osteoporosis and Osteoporotic Fractures in Gastrointestinal Disease. *J Bone Metab*. 2018;25(4):213-217. doi:10.11005/jbm.2018.25.4.213
7. Krela-Kaźmierczak I, Szymczak A, Łykowska-Szuber L, Eder P, Linke K. Osteoporosis in Gastrointestinal Diseases. *Adv Clin Exp Med*. 2016;25(1):185-190.
8. Das UN. Inflammatory bowel disease as a disorder of an imbalance between pro- and anti-inflammatory molecules and deficiency of resolution bioactive lipids. *Lipids Health Dis*. 2016;15:11. Published 2016 Jan 13. doi:10.1186/s12944-015-0165-4
9. Krela-Kaźmierczak I, Szymczak A, Łykowska-Szuber L, Eder P, Linke K. Osteoporosis in Gastrointestinal Diseases. *Adv Clin Exp Med*. 2016 Jan-Feb;25(1):185-90. doi: 10.17219/acem/33746. PMID: 26935513.
10. Cummings SR, Rosen C. VITAL Findings - A Decisive Verdict on Vitamin D Supplementation. *N Engl J Med*. 2022;387(4):368-370. PMID:35939583 doi:10.1056/NEJMe2205993
11. https://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/#h5
12. Hoy MK, Goldman JD. Calcium intake of the U.S. population / What We Eat in America, NHANES 2009-2010, USDA http://www.ars.usda.gov/SP2UserFiles/Place/80400530/pdf/DBrief/13_calcium_intake_0910.pdf, accessed 1-3-21
13. Weaver CM. Age related calcium requirements due to changes in absorption and utilization. *J Nutr*. 1994;124(8)(suppl):1418S-1425S. PMID:8064395 doi:10.1093/jn/124.suppl_8.1418S
14. Heaney RP, Recker RR, Stegman MR, Moy AJ. Calcium absorption in women: relationships to calcium intake, estrogen status, and age. *J Bone Miner Res*. 1989;4(4):469-475. PMID:2816496 doi:10.1002/jbmr.5650040404
15. Heaney RP, Gallagher JC, Johnston CC, Neer R, Parfitt AM, Whedon GD. Calcium nutrition and bone health in the elderly. *Am J Clin Nutr*. 1982;36(5)(suppl):986-1013. PMID:6765074 doi:10.1093/ajcn/36.5.986
16. Manoury E, Jourdon K, Boyaval P, Fourcassié P. Quantitative measurement of vitamin K2 (menaquinones) in various fermented dairy products using a reliable high-performance liquid chromatography method. *J Dairy Sci*. 2013;96(3):1335-1346. PMID:23332840 doi:10.3168/jds.2012-5494
17. Hojo K, Watanabe R, Mori T, Taketomo N. Quantitative measurement of tetrahydromenaquinone-9 in cheese fermented by propionibacteria. *J Dairy Sci*. 2007;90(9):4078-4083. PMID:17699024 doi:10.3168/jds.2006-892
18. Schurgers LJ, Vermeer C. Determination of phylloquinone and menaquinones in food. Effect of food matrix on circulating vitamin K concentrations. *Haemostasis*. 2000;30(6):298-307. PMID:11356998
19. Vermeer C, Raes J, van 't Hoofd C, Knapen MHJ, Xanthoulea S. Menaquinone Content of Cheese. Nutrients. 2018;10(4):446. Published 2018 Apr 4. doi:10.3390/nu10040446
20. Bruno EJ. The Prevalence of Vitamin K Deficiency/Insufficiency, and Recommendations for Increased Intake. *Journal of Human Nutrition & Food Science*. 4(1): 1077.
21. Wallace TC, McBurney M, Fulgoni VL. Multivitamin/Mineral Supplement Contribution to Micronutrient Intakes in the United States, 2007–2010, *Journal of the American College of Nutrition*, 33:2, 94-102, DOI: 10.1080/07315724.2013.846806
22. https://www.drugwatch.com/proton-pump-inhibitors/

23. Daniels B, Pearson SA, Buckley NA, Bruno C, Zoega H. Long-term use of proton-pump inhibitors: whole-of-population patterns in Australia 2013-2016. *Therap Adv Gastroenterol*. 2020 Mar 19;13:1756284820913743. doi: 10.1177/1756284820913743. PMID: 32218806; PMCID: PMC7082869.
24. Hálfdánarson ÓÖ, Pottegård A, Björnsson ES, Lund SH, Ogmundsdottir MH, Steingrímsson E, Ogmundsdottir HM, Zoega H. Proton-pump inhibitors among adults: a nationwide drug-utilization study. *Therap Adv Gastroenterol*. 2018 May 30;11:1756284818777943. doi: 10.1177/1756284818777943. PMID: 29872455; PMCID: PMC5977421.
25. Eshraghian A. Bone metabolism in non-alcoholic fatty liver disease: vitamin D status and bone mineral density. *Minerva Endocrinol*. 2017;42(2):164-172. PMID:27973461 doi:10.23736/S0391-1977.16.02587-6
26. Mawer EB, Klass HJ, Warnes TW, Berry JL. Metabolism of vitamin D in patients with primary biliary cirrhosis and alcoholic liver disease. *Clin Sci (Lond)*. 1985;69(5):561-570. PMID:2996827 doi:10.1042/cs0690561
27. Cotter TG, Rinella M. Nonalcoholic Fatty Liver Disease 2020: The State of the Disease. *Gastroenterology*. 2020;158(7):1851-1864. PMID:32061595 doi:10.1053/j.gastro.2020.01.052
28. Kohlmeier M. *Nutrient Metabolism, Structures, Functions and Genes*. 2nd ed. Elsevier; 2015:507.
29. Chronic Kidney Disease in the United States, 2021 (cdc.gov) available at https://www.cdc.gov/kidneydisease/pdf/Chronic-Kidney-Disease-in-the-US-2021-h.pdf#:~:text=CKD%20Is%20Common%20Among%20US%20Adults%20Fast%20Stats,37%20million%20people%2C%20are%20estimated%20to%20have%20CKD.%E2%80%A0
30. Lv JC, Zhang LX. Prevalence and Disease Burden of Chronic Kidney Disease. *Adv Exp Med Biol*. 2019;1165:3-15. PMID:31399958 doi:10.1007/978-981-13-8871-2_1
31. Zittermann A, Ernst JB, Gummert JF, et al. Vitamin D supplementation, body weight and human serum 25-hydroxyvitamin D response: a systematic review. *Eur J Nutr*. 2014;53(2):367-74. doi:10.1007/s00394-013-0634-3. Epub 2013 Dec 1. Review. PMID: 24292820
32. Pereira-Santos M, Costa PR, Assis AM, Santos CA, Santos DB. Obesity and vitamin D deficiency: a systematic review and meta-analysis. *Obes Rev*. 2015;16(4):341-349. PMID:25688659 doi:10.1111/obr.12239
33. Ekwaru JP, Zwicker JD, Holick MF, et al. The importance of body weight for the dose response relationship of oral vitamin D supplementation and serum 25-hydroxyvitamin D in healthy volunteers. PLoS One. 2014 Nov 5;9(11):e111265. doi:10.1371/journal.pone.0111265. eCollection 2014. PMID: 25372709
34. Yao Y, Zhu L, He L, et al. A meta-analysis of the relationship between vitamin D deficiency and obesity. *Int J Clin Exp Med*. 2015 Sep 15;8(9):14977-84. eCollection 2015. PMID: 26628980
35. Prevalence† of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS (Behavioral Risk Factor Surveillance System), 2020 https://www.cdc.gov/obesity/data/prevalence-maps.html accessed 8-26-22
36. Mohammadi Z, Keshtkar A, Fayyazbakhsh F, et al. Prevalence of osteoporosis and vitamin D receptor gene polymorphisms (FokI) in an Iranian general population based study (Kurdistan) (IMOS). *Med J Islam Repub Iran*. 2015;29:238. PMID:26793629
37. Mercola J, Grant WB, Wagner CL. Evidence Regarding Vitamin D and Risk of COVID-19 and Its Severity. *Nutrients*. 2020;12(11):3361. PMID:33142828 doi:10.3390/nu12113361
38. Simon M, Pizzorno J, Katzinger J. Modifiable Risk Factors for SARS-CoV-2. *Integr Med (Encinitas)*. 2021;20(5):8-14. PMID:34803534
39. Ghelani D, Alesi S, Mousa A. Vitamin D and COVID-19: An Overview of Recent Evidence. *Int J Mol Sci*. 2021;22(19):10559. PMID:34638897 doi:10.3390/ijms221910559
40. Ali N. Role of vitamin D in preventing of COVID-19 infection, progression and severity. *J Infect Public Health*. 2020;13(10):1373-1380. PMID:32605780 doi:10.1016/j.jiph.2020.06.021
41. Whiting SJ, Calvo MS. Correcting poor vitamin D status: do older adults need higher repletion doses of vitamin D3 than younger adults? *Mol Nutr Food Res*. 2010;54(8):1077-1084. PMID:20440693 doi:10.1002/mnfr.200900536
42. Osteoporosis Canada - https://osteoporosis.ca/vitamin-d-supplementation-and-fracture-prevention/
43. Arias CF, Herrero MA, Echeverri LF, Oleaga GE, López JM. Bone remodeling: A tissue-level process emerging from cell-level molecular algorithms. *PLoS One*. 2018;13(9):e0204171. doi:10.1371/journal.pone.0204171