Release Notes 2022-07-28 : This is first a request for data and nominally an attempt to moderate the hype around vitamin D . Last minute literature searches were turning up more works expressing similar ideas, it may not be as novel or controversial as I thought. It describes a more general problem looking at one molecular entity in isolation. The tone is a bit less scientific than some notes, I have cited wikipedia in places, as the debate is quite "mainstream." Other recent molecules getting similarly singled out include amyloid beta [1] as a drug target which despite decades of research has only produced a constroversial drug approval that few actually believe. This work does advance a hypothesis outline and alternative approaches to development. I do give active dogs some vitamin D from time to time. For the sake of disclosure, I became more interested when my mom's situation changed while getting prescription vitamin D. Also note the bibliography was formatted with a developmental tool and may contain bizarre errors. Dates and autnors do not appear uniform but many links are provided with a query string to identify this document to the server. This may annoy some servers but alt links are available. Basically I just got tired of tweaking it for now...

This work addresses a controversial topic and likely advances one or more viewspoints that are not well accepted in an attempt to resolve confusion. The reader is assumed familiar with the related literature and controversial issues and in any case should seek additional input from sources the reader trusts likely with differing opinions. For information and thought only not intended for any particular purpose. Caveat Emptor
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Vitamin D: Towards A Conflict Resolving Hypothesis

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(Dated: July 28, 2022)

Vitamin D remains as a contentious supplement associated with strong proponents, skeptics, and ambiguous data. Proponents often point to association studies suggesting supplements will be beneficial but skeptics contrast these to the less compelling intervention studies. In spite of widespread use, concerns about relative efficacy and safety persist. In continuing controversies, it may help to examine assumptions or refocus the investigations. Correlation that does not translate into intervention should spur more investigation into cause and effect which would hopefully uncover important details. Some considerations in controlled trials include study population, placebo, dosing schedule, formulation, endpoint specifics, and ultimately judgement of the authors. This work focuses on the status of related nutrients and lifestyle factors as they impact calcium distribution which may have subtle health effects . While calcium is often the central focus of vitamin D research, it interacts with other nutrients, notably citrate, and the needs of bone as signalled by mechanical force transduction. Extreme populations, such as astronauts and bariatric surgery patients, can be identified that exhibit "anomalous" calcium handling as reflected in conditions such as urinary stone formation. They may exemplify more subtle conditions in larger populations such as the sedentary or those with subclinical GI impairments or dietary problems.

This works creates some criteria for hypothesis generating data including exceptional populations or documented individuals addressing a role for reduced nutrition or bone stimulation in reducing the vitamin D NOAEL. A cursory look at some vitamin D trials is consistent with this idea but retrospective detailed analysis or a prospective RCT would be needed to make specific statements. Such data may also help motivate a larger role for calcium distribution in excess mortality or morbidity. It may be that the optimum vitamin D intake is modulated by bone loading and distribution of other molecules such as citrate and vitamin K or even calcitonin and gastrin. There is a nacent hint that even tryptophan may be important. Successful interventions may or may not then be primarily an issue of vitamin D control in isolation.

Major Points

1. Correlation v Interventions : Vitamin D may be more of a marker than a therapeutic target. Correlations have been falsely encouraging for vitamin D interventions but they can also be falsely discouraging.
2. Details not just Means : Scatterplots, histograms, outlier details may be informative
3. Patient Specific Factors : Interventions may vary depending on bone loading and other nutritional factors (Species specific factors may be important when looking at implications of non-human data for humans) Speculative new lead to tryptophan .
4. Reconsider Dismissed Factors : Patterns in stone formation and role of gastrin via calcitonin dynamics may be instructive.
5. Request for Data : Human data with information on bone loading an presumed nutrient status would be useful for hypothesis generation
6. Possible Implications if true : Be suspicious of vitamin D in most indications for those without bone loading (including astronauts in good health) or nutrient uptake issues (including many elderly). Instead, try to fix the cause(s).

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1. INTRODUCTION

Despite decades of research, vitamin D continues to be a controversial supplement [111] . So much so, that there is a conference dedicated to controversies [20] with recent topics including inconclusive clinical trials and design limitations [52] [7] . While most overtly associated with bones and calcium, and in fact approved by the USA FDA to treat rickets among other things , association studies have been interpreted to suggest a causal link between intake or blood levels of vitamin D and many health outcomes. However,many interventions have produced equivicable results with many encouraging ad hoc explorations but few meaningful primary ones hitting. Unfortunately this situation is quite common as specific molecules, such as vitamin C or amyloid beta, become trendy. Once a molecule becomes popular, clinical trials tend to test specific hypotheses about the molecule rather than create more data about how it fits into a larger system. This can produce a lot of failures with little knowledge gained and the faulty logic linking correlations to interventions is not revealed. One recent paper captures a lot of the problem while introducing an association between vitamin D supplementation in humans and worse statistics for Alzheimer's disease and mortality[83].

The present work points to latent inhomogeneity in trial populations that needs to be resolved to better understand vitamin D effects. One source of inhomogeneity is initial vitamin D blood levels and patients may be selected for "low" levels as they would be the most likely to benefit from supplements. It has been thought that there is a fixed healthy reference range [77] although there is reason to suspect that optimal levels can vary [1].

Other sources of variability need to be considered that modulate the function relating vitamin D status to clinical situation. Dominant vitamin D effects, both good and bad, are likely to be mediated by less appreciated aspects of calcium disposition. The limited data presented here suggest that important patient variables include mechanical bone stimulation and overall nutrient uptake. Other nutrients are probably important for determining the vitamin D dose-response curve. While important in bone, overt pathological calcium deposits may form in blood vessels and the urinary tract. In the blood, calcium tends to be complexed with citrate. Besides citrate, phosphorous, vitamin K and amino acids along with signals such as "exercise" to motivate bone growth are likely factors. Consideration of PTH [37] may be more important than blood levels of vitamin D metabolites. Special populations with exaggerated and unusual combinations of attributes include astronauts and bariatric surgery patients. Both groups also exhibit distinctive urinary stone anomalies that may relate to vitamin D. While immobilization is known to increase stone formation, questions remains about the overall health of such patients. Astronauts however are selected and trained for good health yet still get stones in zero g [129] . Despite sometimes being dismissed as unrelated to vitamin D, urinary stones may present an opportunity to understand more about Ca fate in context and its clinical relevance. Additional pathways may also need more consideration. Despite endogenous calcitonin being of no clinical relevance in extreme static states, its ancient evolutionary history and relationship to gastrin may be suggestive of larger regulatory roles [49]. If it acts as a regulator of vitamin D in dynamic cases this may be a commonly ignored biological paradigm often described in the literature as a "paradox." Viamin D uniformly becomes toxic at a high enough dose, but it remains unclear how low the NOAEL can become. That is, can "normal" doses of vitamin D become counterproductive in a significant fraction of potential users? A search of prior trials may tend to substantiate or refute this line of inquiry. Supporting evidence would suggest that those who do not transduce mechanical bone forces (the sedentary, bedridden, activity restricted, or with defects in transduction) or some class of nutrient issues (specific diet or GI defects) would be the most likely to benefit from vitamin D restriction and should show up as detractors from clinical trials of higher doses.

Many vitamins are known to be deleterious at high absolute or relative doses and high dose vitamin D is routinely used as a poison. Even folate and B-12, which are generally considered safe, have increased markers of cancer [163]. It is almost surprising that calcium control and vitamin D idiosyncracies have not gotten more attention.

By some indications, trends in bone loss and stone formation appear to be going the wrong way [139] despite all the press on vitamin D and health in general. This text should help determine if vitamin D usage could be a contributor to that problem or not. Readers familiar with the topic may wonder how I got this far without mentioning oxalates but these are included in other nutrients as endogenous production is still a confusing factor.

The present work probes the idea that the vitamin D dose-response curve is strongly patient dependent but modified by identifiable factors including overall nutrition and bone loading. As vitamin D may regulate calcium and citrate distribution, mozilizing both a dangerous precipitator and its chaperone, balances of the two may be crucial to clinical outcomes. However, there is even more to the story of calcium supersaturation and conditions ideal for bone deposistion [106]. The rest of this work outlines important considerations in asking better questions and geting more relevant data on interventions.

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[1] Although internet sites appear to have considered the larger context for many years, one site dating from 2016 was recently brought to my attention suggesting that optimal vitamin D levels can vary [36].

2. VITAMIN D IN VARIOUS CONDITIONS

Significant literature exists on vitamin D for many conditions. The topics included here are cardiovascular disease, respiratory disease including covid-19 , cancer and autoimmune disease, muscle wasting, osteoporosis, ectopic calcification, stones, arthritis, pregnancy and nutrition and bleeding, VDR KO phenotype, and finally all cause mortality. This starts with those less obviously related to calcium, progressing to more common topics, and then onto nutrition. The most clinically interesting however, all cause mortality, should motivate the issues with dose-response curves. As vitamin D is FDA approved for rickets it is generally considered safe and effective for this indication and is not controversial. However, even in rickets, it is debatable if vitamin D per se is an issue as much as intake of calcium, magnesium, and phosphorous [4]. For most conditions, encouraging correlations fail to translate into useful interventions.

Efficacy for cardiovascular disease did not seem supported as of 2019 [9] . A 2020 review of vitamin D supplementation RCT's suggests many rate ratios may be less than unity but not approaching significance [120] which could indicate a variety of things or just be noise. Similarly, little benefit was seen in stroke recovery [112]. This is despite an association of low vitamin D with stroke [150] which may be due to a reduction in vitamin D in response to a stroke [16] . It is quite likely that the dose-response curve is non-monotonic [165] as there is some suggestion of that for calcium supplements [84]. It is worth noting in passing that similar curves for vitamin K exist and demonstrate increasing risk with reduced intake [13] but there is no reason to suspect a positive slope at higher intakes, consistent with my prior work [102] [103].

Generally hypertension intervention trials have not been encouraging [178] [130] but "hope springs eternal" that design errors can be fixed [88] and meta-analyses, especially with subgroup analysis, can continue to find suggestions of efficacy. In one case for those over 50 or obese [59] . There was even a suggestion of it being deleterious for atrial fibrillation [154] (if I read the abstract right) [62].

Associations in respiratory infections include intake and blood levels with various kinds of morbidity [34] but interventions have been less succesful [35] as with asthma trials [82]. Significant literature exists related to covid-19 . An open label study in the UK (CORONAVIT) offering 3200 or 800 or no vitamin D demonstrated no benefits with many patients being retired or having heart disease and approaching counterproductive in at least one test (low dose v placebo OR for covid-19 1.39, CI 0.98-1.97). [69]. One trial among Mexican health care workers demonstrated an important reduction in SARS-Cov-2 infection rates (6.4 percent with vitamin D vs 24.5 without, p¡.0001) but about 1/3 of the participants dropped out leaving fewer than 200, the placebo was cornstarch, and there were imbalances between the groups [170]. One recent meta-analysis for covid-19 related outcomes found benefits for vitamin D supplementation in ICU admissions and mortality [61] as well as a "Co-VIVID" meta analysis [168] but generally these have not shown consistent meaningful benefits [15] [67] [23] although some are still suggesting supplementation anyway [104] [162] . Some smaller studies headline a success but look more like endpoint fishing. For example, one recent result suggested one positive result among many endpoints [74] but that seems to be a correlation not a group difference and the "study objectives" appear to list that as an after-thought. They describe the vitamin D as a water soluble formulation but no similar vehicle was given to the placebo group in case that aids absorption of other nutrients or itself is active. Plus there is a several year age difference favoring the vitamin D group and a confusing but compensating difference in lung involvement approaching significance. Histograms and models may salvage the work.

Interestingly, medical professionals have been cited as large spreaders of overly optimistic recommendations regarding vitamin D for covid-19 [136].

The VITAL trial was in the news again recently for showing some benefit of vitamin D against autoimmune disease [57] after failing to demonstrate much benefit in cancer. An exploratory analysis reached significance for non-obese subgroup leaving an HR exceeding unity (1.05) for BMI at or above 30 [32] . A 2022 meta analysis also suggested benefits for "normal weight" patients with daily vs bolus dosing [78]. Earlier the adverse events were described by stating [94],

> "ADVERSE EVENTS There were no significant differences between the two groups [in the VITAL trial] with respect to incident diagnoses of hypercalcemia, kidney stones, or gastrointestinal symptoms (Table S4 in the Supplementary Appendix)."

However, appeal to table S4 [2] does suggest a small increase in stones approaching significance (HR=1.12, p=.08) with a significant benefit for vitamin D in GI bleeding (HR=.84, p=.02) with no indication of any effect on "easy

[2] https://www.nejm.org/doi/suppl/10.1056/NEJMoa1809944/suppl_file/nejmoa1809944_appendix.pdf

bruising" . The sample size was large and the patient population fairly diverse suggesting that a subgroup analysis on the stones issue may be informative similar to cancer. The bleeding issue did reach significance and should have been explored- possible reasons include imbalance in vitamin K, aspirin, or some prognostic factor or even an additional benefit of D. Bleeding and vitamin D comes up again in postpartum hemorrhage where it is associated with low vitamin D [91] although interventions and a role for vitamin K may complicate the issue. In any case, consideration of incidental observations may start to make sense of many existing inconsistencies and should not be ignored.

A smaller very recent study of vitamin D, fish oil, and exercise in healthy community dwelling people over 70 years old demonstrated some benefits for each against cancers [21].

One study on mice immobilized with staples and fed a low vitamin D diet did show increases muscle atrophy [115] but the measured vitamin D levels appear undetectable and the change in muscle mass fairly small although reaching significance. It is unclear how moderate levels may work, what their overall diet was, or if mice were examined for other health issues. One small study of elderly people did include 100 iu of vitamin D along with amino acids and exercise to improve muscle mass [141] but a role for vitamin D is not clear. Clearly some is needed for bone and muscle development but a dose-response curve under various conditions needs to be to considered.

Even in osteoporosis, where it is combined with a bisphosphonate in the FDA approved product Fosamax plus D, vitamin D has produced confusing results [87] with supplementation of 10,000 IU/day decreasing BMD leading to concerns about net harms [26] or at least concerns about a non-monotonic dose-response curve as noted with CVD [165] . In extreme doses it useful as a rodenticide presumably due to calcium redistribution . It is worth noting that BMD is not a clinical endpoint and indeed on study on vitamin K in post menopausal women found reduced fracture rates with no improvement in BMD [92]. If the osteoporosis dose-response curve is non-monotonic over easily achievable doses, it would be helpful to know how to estimate the curve for each patient.

In other cases of calcium handling, vitamin D appears as a solution and also a problem in part due to a non-monotonic dose-response curve and probably other factors yet to be determined. Two well documented issues include ectopic calcification and urinary stones. Bone requires a protein scaffold, phosphate, and citrate but calcium can also deposit spontaneously or with the involvement of pathogens auch as nanobacteria [29] or viruses [41] [70] [138] [155] . Generally dependence on blood levels is assumed as more direct than relationship to intake including supplements. Much literature highlights a therapeutic role rather than a contributory role for vitamin D.

In general vitamin D appears to be a "double edged sword" [172] in vascular calcification. On the one hand, calcitriol was shown to increase expression of phosphate transporter SLC20A2 to reduce pathological cellular calcification although the authors do acknowledge that in vivo vitamin D is likely to have a "biphasic" role in "soft tissue calcification" [76] . That work however used an osteoblast osteosarcoma cell line .Almost by definition, the cancer cells are behaving pathologically and responses may not be suggestive of any particualr clinical result. However, D3 also increases citrate secretion from osteosarcoma cells [133] and details of experimental conditiosn may matter. In extreme cases of citrate usage for anticoagulation Osteoblasts in vivo also appear to be better regulated, probably by various paracrine mechanisms, that in vitro [12]. Any association would have to be explored in clinical interventions. Even "pathological" calcification may be a backup immune response but good or bad need to be ascertained not assumed. Another work, also acknowledging non-monotonic effects of vitamin D, concluded that, " in early CKD, increase of the local osteocytic production of 1,25(OH)2D, triggered by renal malfunction, may represent a primary defensive response to protect the organism from ectopic calcification by increasing sclerostin and by suppressing BMP2 production." [118].

Case reports exist which include vitamin D deficiency as a putative cause of ectopic calcification. In one case of Bell's Palsy with calcifications, the authors treated with vitamin D and calcium but noted that herpesevirus is often associate with Bell's Palsy and treatments are not always satisfactory due to "unclear pathogenesis" [58]. Herpesevirus and other pathogens are often associated with calcification and it would be difficult to exclude their involvement.

On the other hand, vitamin K dependent proteins have been shown to have important roles in mineralization regulation [119] [161] and vitamin K appears to be safe in arbitrarily high doses. While stome models have failed to respond to vitamin K, it can reverse warfarin related calcficiations in rats [148].

One meta analysis suggested insignificant benefits for vitamin D in stone formation [93] but the only study with more than 5 events was on adenoma patients (with no benefits for cancer reaching significance) who appeared to be taking more calcium and vitamin D in the placebo group [11] although significance of this to the results is not clear. Other summaries point to decreased stone formation among presumed active patients taking vitamin D which is thought to be due to differential oxalate metabolism [159] but groups such as astronauts exhibit high stone formation rates motivating an issue with bone loading. One recent study looking at cobalt and stones suggested that "heavy activity" increased stone risk [177].

Stone formation theories have included oxalate concentrations, other mineral supersaturation such as Ca, Mg, P, and bacteria. The role of vitamin D supplements in stone formation for certain patients remains unclear and a role in oxalate inhibition may be an important determinant in overall effects of calcium supplements but blood levels of vitamin D metabolites may matter,

> "whereas patients in the highest quartile for 1,25-dihydroxycholecalciferol and FGF-23 had significantly higher odds for stone events compared to the lowest quartile [56]. Although elevated calcitriol levels have been found to be deleterious to the risk of kidney stone formation, probably due to a direct increase in urinary calcium excretion, the association between serum 25-hydroxyvitamin D concentration, and thus of vitamin D administration, and incident kidney stone events is yet to be clarified. Studies analyzing a causative role between serum 25-hydroxycholecalciferol and hypercalciuria in any phenotype of stone disease did not find any significant association. However, when only hypercalciuric kidney stone formers were taken into account, a correlation with vitamin D was found [55,105,106]." [10].

Vitamin D has also been considered with respect to osteoarthritis. Meta-analyses suggest little effect [128] but investigation of details and exploratory analyses is quite suggestive. For example, one ref from [128] suggests in the abstract significant opposing dose-response curves depending on the season with summer being favorable while winter adverse for higher vitamin D levels [81] possibly relating to activity levels which could be confused with sun exposure per se depending on exactly what is measured. Generally benefits in winter are thought to be due to reduced sun exposure.

Some studies have found involvement of calcium in osteoarthritis. An inverse relationship between serum calcium and osteoarthritis approaching statistical significance [90] was observed and calcium crystals in the cartilage of patients have also been noted [158]. However the relationship to bone health and remodelling is not clear [73] [64] .

Pregnancy is one extreme condition that modulates everything from nutrition to clotting to the immune system. Here too early indications are that vitamin D status may associate with outcomes, have some effects, but interventions have not clearly shown a benefit. A recent Cochrane review did suggest some possible benefits [127] . Vitamin D has recently been linked to amino acid transporter LAT1, which antiports tryptophan among other amio acids [145] in preeclampsia [68]. Despite association studies to the contrary, interventions during pregnancy with higher dose vitamin D may have even caused harm in subsequent childhood neurodevelopment [144]. One work from 2015 recognized the discrepancy and found faults in study designs and cited the unique nutritional issues with pregnancy [75] while presuming there must be some beneficial effects that just need to be proven. This work did not appear to consider that the correlations simply point to correlated nutrients like other lipophilics including vitamin K that are at least as important to getting clinical benefit.

Vitamin D receptor KO mice have been cited as demonstrating effects of vitamin D deficiency even as differences between expression and vitamin D status were emerging [24] . Alopecia, which is "not observed in vitamin D deficiency", appear to depend on the expression of the receptor rather than its ligation (with vitamin D) status and most defects, although not alopecia, can be overcome with calcium and phosphate normalization [46]. This work also suggests that phosphatemia may regulate apoptosis of hypertrophic cells or at least chondrocytes and that the receptor assists osteoclastogenesis. Receptor and transporter deployment regulation is one concern in aging and regulation may depend non-intuitively on nutrient intake and digestion. Indeed, receptor KO mice are more resistant to at least one intestinal challenge [153] suggesting receptor down regulation may be adaptive.

Maybe most generally, the relationship between vitamin D and all cause mortality in older people appears to have the same issues. Popular perceptions like those reflected in the wikipedia entry for vitamin D [175], may even reflect the existence of a maximum in the dose-response curve . Much literature exists but again trying to conflate correlations with interventions. One very recent work summarizes the problem with supplementation for the elderly discussing dementia correlation with supplementation and non-obvious effects of the VDR and all cause mortality [83].

Supplementation trials have shown some arguable successes. For example, a 2007 meta analysis suggested supplements improved all-cause mortality and the compliance may be a factor in reducing success [8]. One reported success of supplementation on all-cause mortality was not an RCT but simply an observational study on patients at the Veterans Health Administration who were prescribed vitamin D at some point [5]. Other recent critical appraisals of RCT's begin with many caveats on study design while tending to suggest the correlations strongly suggest vitamin D must do something but recognize interaction with other nutrients including vitamin K (and A and magnesium) [131].

Observational studies may have been more encouraging and those with large sample sizes may allow for better "mean" dose-response curves to be estimated. A 2021 observational study of UK CVD patients found a monotonic relation between blood levels of vitamin D and outcomes including all cause mortality [42] a similar result to that found in 2008 [110] but the correlates including age and exercise may not have been adequately explored.

A 2021 work tried to estimate "a" dose-response curve for vitamin D levels and various outcomes including all cause mortality finding an optimum [167] but with increasing hazards in either direction. At least one review from 2022 begins to consider the possibility that optimal vitamin D levels vary importantly between outcome types such as all cause mortality versus specific outcomes [55]. Genetic sources of variability between patients have also been explored [31].

3. CONFOUNDERS

Several patterns emerge from both the vitamin D literature and contemporary and historical medical controversies. The inverse problem [174] of identifying a complex system based on a few input and outputs, is ambiguous but some progress may be possible with simple approaches and past experiences from failures and known biological system topologies.

3.1. Associated or Correlated Variables

One source of difference between works is the actual "amount" of vitamin D being associated with some outcomes. There is recognition that intake is not well related to uptake due to digestive or other issues. A conceptual forward pathway may be outlined as,

$$UV, diet \rightarrow D3 \rightarrow 25OHD \rightarrow 1,25(OH)_2D \rightarrow VDR \tag{1}$$

with everything from sunlight to VDR concentration in addition to intake , being related to an outcome often thought to be mediated by VDR activation. More detailed analyses exist , for example [132], but this captures the common ones. The major circulating molecule 25-OH D, is not particularly active and is not directly related to VDR occupancy or vitamin D activity or velocity. Notably, 25-OH D does not correlate well with athlete bone health as osteogenic stimuli are thought to be bigger factors [126]. Conversion of 25OHD to the active $1,25(OH)_2D$ occurs at a rate not necessarily related to blood levels. The circulation of an inactive precursor is a common paradigm. Total synthesis may be slow and complicated but cleavage or a single modification with readily available group can be fast and simple.

Some Vitamin D's and Related Molecules	
shorthand	notes
D_2	ergocalciferol
D_3	cholecalciferol
$25OHD$	circulaing, unrelated to bone health [126]
$1,25(OH)_2D$	calcitriol active
$1,24(OH)_2D$	similar to calcitriol
$24,25(OH)_2D$	
PTH [37]	parathyroid
calcitonin	thyroid, limited static effects

TABLE I: Summary of the vitamin D related molecules that may be relevant to overall "status". Various sources [19]

Related entities that may be measured or manipulated include PTH and calcitonin. PTH appears to be largely a response to "ionized' calcium [79] although blood calcium may be free or complexed with citrate.

Beyond this, correlations between D status variables likely exist with other nutrients due to intake and uptake issues. Notable variables include vitamin K cycling activity, citrate dynamics, and amino acids as well as calcium and phosphorous.

Conversion and clearance rates may also be contributors to blood levels and rate equations, outlined in the Discussion section, should be estimated before concluding much from correlations. Blood levels may or may not be regulated but they need not reflect intake. In the case of amino acids and SMVT substrates, "altruistic export" may raise blood levels even as nutrient stress is encountered due to transport to the brain or other locations [99]. Redistribution is common and dynamics may be complex. Vitamin D blood levels are thought to be decreased in response to stroke [16] but without knowing why it is unclear if more intake would help.

3.2. Intervention and Placebo

Trials vary greatly in intervention and control protocols. Interventions are often oral with vitamin D formulations of variable complexity. Placebo may or may not reproduce the overall active intervention up to the (small) vitamin D component. One concern is emulsifiers or even oils that can assist absorption of vitamin D and may produce effects that are most apparent in damaged GI tracts allowing more nutrients to be imported and contribute to apparent benefit of vitamin D. Vitamin D formulations remain as an active area of research [85] and it is important to remember, especially in those with GI impairments, that any vehicle to assist vitamin D absorption can have effecs on other nutrients and the vehicle has to be part of at least one control arm ideally with another placebo. Sorbitol, for example,

may be common in foods but in certain combinations is thought to enhance extraction of many relevant substances [25]. As part of a vitamin D formulation it may change many nutrient uptake values. Solubility and availability have been addressed in other recent works simply trying to optimize dog foods [98] with less obvious possibilities such as deep eutectic solvents [97] considered too. All of these components may have physical and metabolic properties that may be significant.

3.3. Populations

Special populations with extreme attributes may help resolve remaining subtle issues with vitamin D in nominally normal populations. Astronauts experience microgravity among other stresses and have significant known problems with osteopenia [51] and calcium stones even post-flight. Exercise, potassium citrate, bisphosphonates have been evaluated [53] but the problem appears to persis . Indeed, the comparison between aging and space flight has been considered

> An optimized diet [105,106] helps to mitigate bone loss with little risk of side effects by providing adequate amounts of calcium, vitamin D, and vitamin K in the space diet [107]. Many parallels have been found between nutritional orthopedics and space nutrition because of the similar challenges faced by an aging orthopedic patient on Earth and an astronaut experiencing the degenerative effects of long-duration space missions [108]. A daily balance of fiber, liquids, and bioactive substances, such as coffee, is necessary to prevent hip fracture when transitioning from a low-gravity field to hyper-gravity while landing on a planet. [48]

although that text goes on to glibly recommend "Increase Vitamin D Intake." It is also important to remember that space flight conditions vary in many ways leading to other problems such as urinary retention [157]. Recommended vitamin D for astronauts has been about 800-1000IU/day [51] but it is not clear how much testing was done. Bariatric surgery patients have broad changes in vitamin absorption as well as changes in bone loading due to weight and mobility issues. Bariatric surgeries create some interesting data demonstrating increased stones associated with absorption reduction such as RYGB but decreases with restrictive measures such as banding [143] with different post-surgery nutrient uptake profiles [50]..

GI damage can be suspected of reducing vitamin D uptake but it may act more broadly effecting clinical outcomes. For example, chronic pancreatitis is associated with increased risk of urolithiasis [33] which could be consistent with a nutritional cause although oxalate absorption per se is often blamed.

3.3.1. Dose-Response Variation

It is generally accepted that "high enough" doses of vitamin D will be pathogenic and tolerable upper limits have been investigated [109]. It is possible that the dose-response curve for vitamin D is a strong function of patient state and common situations can reduce the effective NOAEL[3] for specific patients. This brief discussion is for illustration and more details can be filled in in response to specific data sets.

Randomization and the central limit theorem are used to avoid dealing with specific cases in large trials but the trial inclusion criteria need to be specific enough to test a tractable hypothesis and ultimately write a label for the product . In the extreme but realistic case, where part of the population benefits and part suffers from the supplement, it is likely histograms, survival curves, or scatter plots will reflect this. Survival curves may differ qualitatively and not exhibit proportional hazards between groups. This can be dealt with in more detail once a suitable data set is obtained with a general analysis validated against at least one usable example.

The path from input variable to output variable may be quite complex. Often intake is recognized to not correlate with blood concentrations, the latter may be adaptive or just uncontrolled or represent transport. Interventions generally include vitamin D supplements, often oral, with outcomes being biochemical (blood D, calcium, BMD, etc) or clinical (all cause mortality, fractures, etc). The case considered here is a bit abstract with details waiting a specific data set.

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[3] This may be a slight abuse of terminology as the question exists about "observed." I amusing this for shorthand for " lowet dose to be worse than placebo " even if the damage is not ovservable without great effort.

Thinking outloud
These are for illustration only serving as placeholders until specific data sets can be analyzed. Spot checked "R" output for consistency with equations here but no assurance of typo correction and algebra accuracy.

Consider the case of a trial with two groups, placebo and treatment with the latter getting some dose "d". The response could be a more or less monotonic biochemical response such as blood or urine calcium levels at some time point. Or, it could be a clinical endpoint such as interval until death which is likely a non-monotonic function of dose and patient specific parameters. In the latter case, knowing that higher doses of vitamin D are toxic, consider the case of a deterministic dose-response curve dominated by saturating first and second order effects,

$$r = r_0 + \frac{c_1 d}{1 + b_1 d} - \frac{c_2 * d * d}{1 + b_2 * d * d} \tag{2}$$

The first order response it assumed to be beneficial while the higher order is a detrimental "side effect." Parameters are arguably patient specific. This yields zero net benefit at

$$d = \frac{-c_2 + \sqrt{c_2 * c_2 + 4 * c_1(c_2 * b_1 - b_2 * c_1)}}{2(c_2 * b_1 - c_1 * b_2)} = \frac{-c_2 + c_2\sqrt{1 + 4 * \frac{c_1}{c_2}(b_1 - b_2 * \frac{c_1}{c_2})}}{2(c_2 * b_1 - c_1 * b_2)} \tag{3}$$

where $r0$ is the "response" to placebo, the second term is a saturating first order term that could model the intended therapeutic effect, and the final term a "side effect" or adverse response that explains toxicity at higher doses. Note that in reality there is probably always a zero-benefit dose (a NOAEL if you "observe" closely enough) but with these parameters it could become complex at

$$b_2 = \frac{c_2}{c_1}\left(b_1 + \frac{c_2}{4c_1}\right) \tag{4}$$

and a better choice of parameters could be found. More realistic curves may derive from products as "everything has to go right" to get a maximum clinical benefit. In this case, perhaps something similar to

$$r = \left(r_0 + \frac{c_1 * d}{1 + b_1 * d}\right) exp(-d/d_c) \tag{5}$$

where d_c is some critical amount.

Similar probability distributions could be made taking the above as an expectation value and adding some deviations,

$$P(r; d) = Aexp(-(r - < r(d; r_0, b_1, c_1, b_2, c_2) >)^2/\sigma^2(d)) \tag{6}$$

In reality the body has some background level of vitamin D and replacing d with "$d - d_0$" may be more appropriate. As stated there are already a lot of parameters relative to likely data and a better constrained model may be useful with specific data. A trial generates two or more sets of r's - one for each group - although often the means or similar results are compared without looking at the distributions. Measured prognostic imbalances may be related to r_0 but the point here is that the dose related parameters can change too. Within this model, the parameters of concern are c_2 and b_2 which may relate to calcium dynamics.

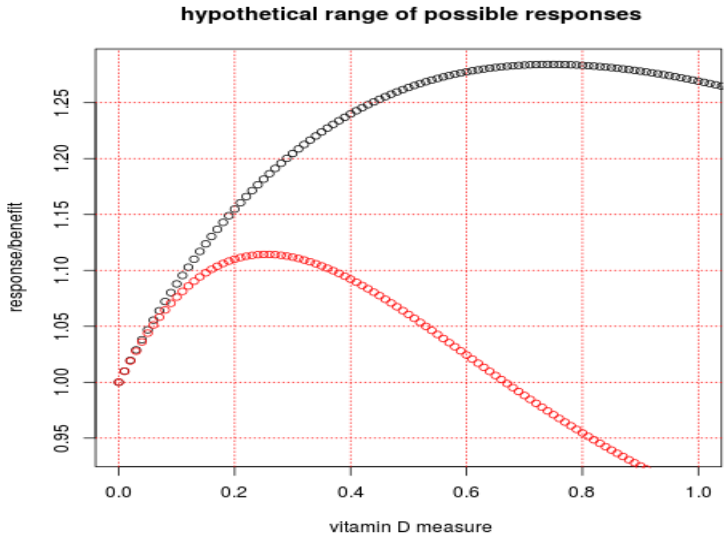

FIG. 1: Range of hypothesized responses to vitamin D for various patients. Note deleterious response at moderate doses (red curve, c2=b2=1.5) that benfit others (black curve,c2=b2=.3). Parameters common to both curves are r0=b1=c1=1.

The hypothesis then is that the parameters vary meaningfully among normal patient populations. It may be possible to measure nominally monotonic non-clinical endpoints like blood calcium versus vitamin D intake and find a non-monotonic relation between [Ca] and life expectancy ultimately relating d to r. However, measuring all-cause mortality vs "d" would be more direct.

This hypothesis outline would be supported if the outcome histogram separated as dose increased over a relevant range although this is not a specific finding. Ideally the outcomes would resolve into well separated groups that could be identified by some prognostic variable such as nutritional status of bone loading.

The argument is further motivated by consideration of certain extreme populations with clear perturbations of calcium dynamics.

3.3.2. Immobilized/ Zero G no bone loading

Bone loading is likely a big contributor to calcium dynamics and several populations exist that vary in actual forces put onto bones that could stimulate growth. In the terrestrial setting, most reduced bone loading is related to some other pathological condition but in zero G astronauts typically are trained and selected for overall health.

As early as 2002, analysis of space mission bone and calcium issues pointed to vitamin K as a bigger issue than vitamin D [60] One result from 2005 suggested vitamin D was ineffective but vitamin K may have some effect on bone resorption in astronauts based in part on results with tail-suspended rats [66]. As of 2021 it seems to be gaining prominence as an important part of flight nutrition [160] . Non-ambulatory status was a large risk factor even for metabolic bone patients [149].

Integrin defects that prevent mechanotranduction may be instructive [134] as well as roles for various calcium sensors [147]. Interestingly, CaSR comes up in other contexts and may be tryptophan inducible [56] with a possibly related role for IDO in avoiding arterial calcification [125]. This is a very exciting specualtive lead because it gets to my earlier concerns with aging [100] [101] and unpublished elaborations thereof. Calcium precipitation may be a useful strategy to avoid aberrant signalling due to Ca leak around missing tryptophan in membrane spanning proteins.

3.3.3. Bariatric Surgery

Bariatric surgery is designed to redice patient weight by altering the processing of food and ultimately the nutrient uptake [146] . It is thought that slower more subtle digestive changes occur with old age [151] when vitamin D is thought to be important for bone health. Significant literature for bariatric surgery exists on bone health as well as larger nutritional issues with some clear distinctions between the restrictive and mal-absorptive procedures. This has been summarized as follows [14] ,

> Many studies have shown significant declines in BMD and BMC during the first year following BS (89), but accumulating evidence suggests that the negative effect on bone is dependent on the type of surgery (12). In their recent systematic review, Rodriguez-Carmona et al. (13) found that patients who had undergone malabsorptive BS (BPD-DS, RYGB and long-limb RYGB), but not restrictive procedures [vertical banded gastroplasty (VBG), AGB and SG], had significant BMD deterioration in several sites during the first postoperative year. However, the majority of the published literature comprises studies with relatively short-term followup among RYGB patients, with fewer studies of other types of BS (12), and other studies have demonstrated negative skeletal consequences following restrictive procedures as well (14, 15).

As an extreme and sudden event, it creates an exaggerated reaction to nutritional changes that can be compared and contrasted to varying degrees with old age and other potential conditions addressed with vitamin D. One distinctive side effect is changes in the risk of developing urinary stones. Stone risk with high vitamin D levels remains as a concern although debate remains about toxic levels of D. A 2016 review of nephrolithiasis and bariatric surgery detailed several factors that may contribute to the observed risks after surgery [18]. Interesting observations include a clear procedure specific risk with increases for malabsorptive approaches but decreases for restrictive ones. This is despite reduced uptake and urinary calcium for RYGB [173]. Vitamin D deficiency is thought to occur.

Most of the analysis concentrates on oxalates. but dynamics of oxalates may not be obvious. Oxalate sources include diet and endogenous production from metabolism. Dietary protein is generally not thought to be a significant contributor to urinary oxalate although some controversy remains [80]. Oxalate transport may relate to anion transporters that also handle chloride, bicarbonate, and sulfate [63]. Interestingly, many other ions can dissolve precipitates and chloride and sulfate may be suspected for this.

Bariatric surgery patients presumably have at least two changes: nutrient uptake and bone loading. Bone loading after successful surgery may be reduced by weight loss or even increased by activity increase. However, stone formation appears to depend on the type of surgery.as the bypass people seem to have more stones whiles the restricted fewer. One concern with digestive system is saturating the acid production capacity and reduced stomach loading may actually improve digestion helping nutrient balance. The throttled entry of food into the GI tract may avoid overloading digestive capacity to generate acids or enzymes allowing for more complete ("balanced?") absorption of whatever makes it through. This may make a case for normal people to eat small meals continuously but a better solution may be to add digestive aids to less frequent larger meals. The bypass patients have known nutrient deficiencies including lipphilics. Often stones are just considered in terms of oxalate output but other nutrients may be relevant too. Important nutrients to consider include calcium and phosphorous but citrate, vitamin K, and amino acids. Importantly, vitamin K does not seem to have a maximum tolerable dose of any significance in contrast to concerns with vitamin D.

4. DISCUSSION

Vitamin D is approved by the US FDA[4] for for the treatment of rickets, secondary hyperparathyroidism with low serum vitamin D(RAYALDEE) , in combination with bisphosphonate for osteoporosis (FOSAMAX PLUS D) and some amount is needed for optimal health. Beyond these indications, the vitamin D literature demonstrates a lot of correlations between markers of vitamin D status and clinical health. but fails to show interventions as clearly beneficial. Existing data and theory motivates interest in interactions between other factors such and diet and lifestyle over a broad range of genetics.

Blood levels of some vitamin D metabolite are often cited as part of a case linking vitamin D to health. However, blood levels of anything are governed by rate equations for production and removal and either side could change the steady state levels. Levels of many blood components may respond to diverse inputs and some may even increase concomitant with overall supply shortages in the case where nutrients need to sacrificially transported to the brain [99]. To focus the discussion, a simplified first order non-saturating rate equation may be helpful such as,

$$\frac{dD}{dt} = \phi_{internal} + a_{uv} * \phi_{uv} + a_{diet} * \phi_{diet} - \frac{1}{\tau} D; \frac{1}{\tau} = \sum \frac{1}{\tau_i} \tag{7}$$

where "D" is a blood level of some form of vitamin D (ignoring factors like blood volume etc). The steady state level is then ,

$$\tau(\phi_{internal} + a_{uv} * \phi_{uv} + a_{diet} * \phi_{diet}) = D \tag{8}$$

[4] I can not find a good single source that states this at any point in time but what I could find from Drugs@FDA

. This appears to show that with negligible input/conversion from internal stores, it is directly proportional to intake. However, the input from any reserves , the "a" coefficients, and τ may change from pathological or adaptive responses. And in reality control over the input and return to internal stores is ignored but likely important.

PTH for example may modulate some of these constants with details depending on exactly what "D" is being explored [79].

Various works have made quantitative models of parts of vitamin D metabolism [169] [108] including half-lifes of vitamin D metabolites in various populations [72] with pharmacokinetics in the toxic region [71] also available. However, it is not clear if variations in healthy blood levels have been explored. Storage appears to be largely in adipose tissue with similar concentrations among obese and non-obese but with significantly higher total capacity suggesting more needed to saturate the fat depot [28] as has been a concern for other fat soluble nutrients including vitamin K and amino acids such as tryptophan or tyrosine.

Blood level increase with vitamin D supplements may not mean that the vitamin D matters but rather can just serve as a prognostic factor. It would suggest lower than normal endogenous production and intake but that the GI tract is functioning and that blood levels may not be strongly down-regulated (decreased lifetimes). This is consistent with the absence of pathological states tending to reduce vitamin D in the blood. Failure of blood levels to respond to vitamin D supplements may suggest a pathological conditions such as limited GI function. Endogenous production or removal may be regulated in an adaptive manner due to some pathological state. So, while it would appear that increased blood levels correlating with better outcomes implies causality, that need not be the case.

Re-regulated vitamin D levels are not entirely hypothetical as they have been observed. A work considering reverse causation between covid-19 and vitamin D levels noted an acute decrease in response to controlled endotoxin exposure and considered the larger possibilities [171]. Reduced vitamin D blood levels with decreased Ca absorption and increased losses were seen during bed rest [86], apparently changing the "a_{diet} and $\frac{1}{\tau}$ terms. This is plausible as an adaptation to reduced bone loading. Interestingly, whole body vibration, presumably stimulating mechanotransducers, has been proposed as a means to overcome lack of exercise and even a poor diet [164]. Vitamin D blood levels may also be decreased in response to stroke [16]. A recent analysis of vitamin D in covid-19 discusses many vitamin D metabolites and points to hypocalcemia in other cases and "acute phase " effects on DBP but does not consider vitamin D levels to be adaptive or explore rate equations [132].

Thinking outloud
move this somewhere

Similar response to to reduced citrate or other components necessary for safe calcium handling could be hypothesized as a way to modify calcium distribution. Dicken's early work on citrate in bone from the 1940's was summarized with him suggesting that [54], "... the presence of citrate in bone is crucial for preventing calcium precipitation, either when bone tissue is resorbed in response to lowered serum calcium or when the biomineralisation process starts" recognizing that bone formation is an active particular process and does not benefit from spontaneous calcium deposition [5] His results are corroborated by today's materials scientists growing bone artificially. Interestingly, VDR has been observed to go to the mitochondria and regulate a metabolic switch in cancer [105]. D3 increases citrate secretion from osteosarcoma cells [133]. In extreme cases of citrate usage for anticoagulation in renal procedures (vs dietary citrate), interactions with Ca and PTH etc have been explored [22]. Vitamin D is thought to promote hypercitricemia [40], helping to reduce free vs chelated Ca, although details of regulation remain to be elucidated.

While past analyses tend to assume vitamin D intervention should work given correlation studies, that presumption has to be tested more thoroughly. Observational studies related to vitamin D should observe correlations with at least one other variable for context. The second variable may naturally suggest a "negative control" but that may not exist and a "positive control" or other putatively related vitamin would be imformative as a comoparator for context and hypothesis formulation. Classes of comparator molecules would depend on hypothesis. GI or dietary probably may not just effect one nutrient and the health-limiting nutrient may vary. Discordant patients, those with isolated deficiencies may make stronger evidence for a given nutrient's cause-effect situation. Lipid soluble nutrients such as vitamin K or even amino acids such as tryptophan may be considered. Indeed, some studies with both D and K exist.

Tryptophan is not often considered in the context of vitamin D but it is a lipophillic nutrient with difficulty wetting and a possible segregation issue [96] making it a good suspect for correlating with vitamins D and K as another confounding factor. Additionally, it is known to be destroyed via IDO in times of pathogen attack similar to what is thoought to occur with vitamin D levels in some cases. While very speculative so far, it is an excellent low risk lead to pursue - even if not relevant to vitamin D it is likely a factor in many indications. Vitamin D is also thought to increase expression of ACE-2 [39]. While interpretted as somehow being therapeutic against SARS-Cov-2 , it would

[5] I like to compare this to CVD diamond growth where the diamond is purely carbon but the key is the quality not just accumulation of soot. Here, you want bone not chalk.

also make sense if it helped anticipate a need for tryptophan with the activation of interferon gamma although the cause-effect is not real clear.

While often trial results are reported by group mean or hazard ratio, more generally an intervention can be evalauted as a mapping from one probability distribution of outcomes to another given some patient population. Outcome histograms would hopefully decompose into a sum or convolution of narrower ones distinguished by factors discussed here. A failure to change the mean but with the creation of a bimodal distribution from a unimodal normal suggests a hidden variable in the samples that may be the basis for a better hypothesis. In this case, if the dose-response curve varies and the origin can be ignored, there could be a dose-dependent change in outcome distributions even if means remain similar. Means would be statistical results of population sampling fluctuations. At small enough doses, likely few patients may suffer but at higher doses the distribution of outcomes should spread and eventually extend to both extremes from the control group.

The relationship between groups would be described by the staistics of the dose-response curve parameters. At a minimum, some thought about patient specific dose-response curves should be stated. Those with no bone loading such as astronauts, the non-ambulatory, those with nutrient uptake issues, or in special nutrient flux modes such as pregnancy may be distinguishable with the right data. The elderly and cognitively impaired may be of concern for vitamin D supplementation. Other conditions that can disturb calcium parameters include malignancy and granulomatous disease [137]. Subgroup analysis is ofen employed to find efficacy when a primary endpoint fails allowing for later testing in a better defined RCT. Even more compelling would be a search for safety signals that could be associated with specific patient categories.

One interesting hypothesis from 2006 suggests that vitamin D toxicity may even be influenced by vitamin K [107] and that should be easy to test with markers for vitamin K function (although this seems questionable [121]) and empirically. Calcium chelaters such as citrate or amino acids for creation of high quality bone scaffold may contribute too.

Dietary interactions can be very obscure. Recently I have been looking at benzoate as this may be a solubility and absorption modifier of relevance to lipophilic nutrient uptake. Benzoate occurs naturally in berries [27] and diet soft drinks but has been controversial for 100 years [3] [2]. Possibly uptake of many drugs [6] is influenced by inciendnetal like this. Sorbitol is another uptake enhancer common in vitamin D formulations and it needs to be included in a placebo.

Although some studies have tended to minimize the concern with stones, the role of vitamin D in stone formation remains unclear. It is important to look at marginal signals even if they don't initially quite get to significance. Stones and bleeding may both be vitamin D related issues for example . Oxalates get a lot of blame for stones although endogenous production is still being elucidated it derives from metabolism of "other nutrients". Availability of other small anions such as chloride, sulfate and bicarbonate may be factors. Bicarbonate is a possible metabolite of citric acid. Excess chloride is diet will ulrimately end up in the urine or feces and may increase urinary Ca vs say bicarbonate [114] but if it competes with oxalate that may limit uptake and help dissolve solids. In dogs and cats increased dietary NaCl may be helpful in stone formation [135] as with ammonium chlodre . The role of sulfur containing anions has been under investigation [140] .

If bone loading is an important signal for calcium and vitamin D homeostasis, it is not immediately clear what immobilized or zero-g subjects should target for vitamin D status. While potassium citrate appears to have been part of the research on astronaut diets, it is not clear how much has has focused on vitamin K or a reduction in vitamin D. No indication was found that tryptophan has been explored. An interesting open-access book mentions astronauts in passing but mentions protein and vitamin K re bone health [123] . Vitamin K is also being explored along with vitamin D control in CKD related calficifcation [116] .

Vitamin K has perhaps more pronounced associations and interventions with antagonists have proven deleterious [166] . An observational study found all cause mortality was worse among those with combined d and k deficiency [43] but a better approach would be to look at these as continuous variables and explore correlation and discordant outliers.

Things can also go wrong in vitamin K clinical trials. Previously, I had advocated a "take your best shot" approach [98] where multiple molecules may be combined for various reasons. However, compromise and combination of new entities with things that "kind of work" can may create a false sense of safety and inhibit the molecule being investigated. One recent intervention trial combining 720 micrograms of K2 and 25 micrograms vitamin D failed to show improvement in aortic calcification [47] but there was a high use of statins [176] [65] which may impact utility of K [179] [122] , as well as anti-platelet therapies and DOAC's. In any case there was no indication of significant adverse events related to the vitamin K even as some patients had existing atrial fibrillation etc. Possibly the vitamin D was sufficient to reduce the benefits. While DOAC's do not directly antagonize vitamin K, the potential for coagulation dysregulation exists. Replacement of antagonists with 2mg K2 and 10mg rivaroxaban did not see obvious calcification benefits although figure 2 does show a visual indication of a non-significant improvement [45]. It is not difficult to find cases where anti-coagulants increase mortality, for example [30], even when used according to best practices.

Non-clinical endpoints or otherwise limited data can be a problem and hopefully future work will validate the clinical benefits of unencumbered vitamin K [102].

Although the clinical relevance of static levels in humans is questionable [44] , perhaps calcitonin, possibly an antagonist of vitamin D in Ca absorption [124] , may be a better focus especially when trying to preserve BMD in the absence of mechanical signals. It has an interesting interaction with gastrin and history of incomplete knowledge of control paths. As osteoporosis, popularly associated with vitamin D, is common in old age, the calcitoin - gastrin connection helps relate to previous work on aging related to nutritional defects [100] [95]. While of no known significance at this point, it is interesting that calcitonin receptora peptides contain the "WxxWxxW" motiff [117] and in particular WDGWLCWDDT appeared common. Possible significance would relate to defects that could occur if these motifs are not faithfully translated as may occur with a tryptophan deficiency. Motifs that require more tryptophans would be susceptible to higher powers of trp infidelity. These may be sites of mannosylation (thought to occur in maybe "18 percent of human secreted and transmembrane proteins) [152] , some other conserved function, or of no significanace at all. Ribosomal stalling may be suspected under tryptophan stress [142] but it is unclear if 3 or 4 in a row have special significance.

Calcitonin may also be a good example of a dose-rate effect on response that is likely present but missed in other cases. Although analogs of the human calcitonin may be more effective [44]. Recently, an association was found between calcitonin level and Ca during the rapid bone growth of childhood [156]. Interestingly, while investigating factors effecting calcitonin, it was noted that copper and zinc may inhibit bone loss [89] again motivating concern for larger nutrient issues.

A 2005 work suggested that gastrin secretion could increase after either calcium or amino acid ingestion with more response observed in absorptive hypercalciuria patients [17] which apparently was not stimulated with protein. This supports use of amino acids where digestive secretions may be limiting although appearing to suggest worsening of hypercalciuria. The response to Ca would be adaptive but response to amino acids and not proteins is surprising as protein digestion would seem to be a good stimulus. It is possible however that dietary amino acids could stimulate calcitonin secretion and help correct Ca distribution problems. Attempts the treat a thyroid problem with vitamin D may then be futile in the absence of vigorous bone loading.

It may also be useful but less direct to consider the evolution of mineralization. Mineralization is observed in marine phytoplankton of uncertain fitness improvements [113]. Fish have both cellular and acellular bone [38] the latter perhaps vaguely similar to ecotopic calcification in people. The bone loading in a marine environment is entirely different from terrestrial and many adaptations had to occur during the transition however artifacts of the marine life may persist. Possibly the lack of bone loading creates strong signals to reduce mineral content for some reason favored by ancient evolutionary constraints.

Personal experience, some published in draft form other observations not yet published, would support broader supplementation for large classes of dogs and people. Vitamin D may have some role as may other vitamins in excess of nominal "RDA" values, but contribution to function of a complex feedback system needs to be considered. The case with anti-oxidants was always, " damage must be bad" and preventing it was good but there was a lot more to the story that only became interesting after failed clinical trials. The first effects discovered form a moleculte may not even be the dominate ones.

5. CONCLUSIONS

This work has started towards a hypothesis and actively requests existing or future data to explore specifics. The continuing confusions over the role of vitamin D supplementation may begin resolution with exploratory data analysis rather than repeated testing of similar ill formed hypotheses. Correlations without corresponding successes in interventions should motivate a search for feedback or regulatory pathways or other mechanisms that create the correlation. Subgroup exploration of existing trials based on bone loading and overall nutrient uptake may help elucidate confusing results with vitamin D intervention trials. Besides group averages, histograms and scatterplots, correlations with other things, are available to help distinguigh distinc population components. The main target of vitamin D, calcium, is both necessary and hazardous similar to glucose. Safe handling to avoid ectopic deposition and leaks likely requires many other things that can be found in the right data. Probable nutrients effecting the vitamin D dose-response curve include citrate, phosphate, amino acids, and vitamin K. This work has additionally found specific motivations to have interest in tryptophan which may not have been previously recognized. Marginalized issues such as stones and calcitonin may also be fruitful areas of investigation. Absorption enhancers may be common in vitamin D formulations but not appreciated more generally for therapeutic and placebo/control applications. Further work with sorbitol may add to ongoing work with benzoate. Taking "your best shot" [98] or combining factors thought to matter would be a lot more informative especially with large enough sample sizes to resolve any multiple populations within a sample. In the meantime, existing considerations point to more care when giving vitamin D to the immobilized or

those with other GI or dietary problems.

6. SUPPLEMENTAL INFORMATION

6.1. Computer Code

```
dplot<-function(d, r0,c1,b1,c2,b2)
{
det=c2*b1-c1*b2
print(paste("det",det))
det
disc=c2*c2+4*c1*det
print(disc)
zed=(-c2+sqrt(c2*c2+4*c1*det))/2/det
zedzed=c1/c2
print(zed)
print(paste(" zero benefit dose ",zedzed))
t1=c1*d/(1+b1*d)
t2=c2*d*d/(1+b2*d*d)
r=r0+t1-t2
r
}

d=(0:1000)/100
r0=1
c1=1
b1=1
b2=3
c2=3

r1t<-dplot(d, r0,c1,b1,.5*c2,.5*b2)
r1c<-dplot(d, r0,1,1,.1*c2,.1*b2)
plot(d,r1c,xlim=c(0,1),main=" hypothetical range of possible responses", xlab=" vitamin D measure",ylab="
    response/benefit")
points(d,r1t,col="red")
grid(col="red")
```

p1.R : R code used to make the dose response curves

```
echo -e load /home/documents/latex/proj/vd vd \\ndump\\nmake\\nsave xxxx.bbl | ./mjm_bblfix.out 2>&1 | tee
    xxx
```

Command used to generate the developmental bibliography.

7. BIBLIOGRAPHY

[1] . Faked Beta-Amyloid Data. What Does It Mean? (-) src:www.science.org.

[2] **Minisola , Salvatore and Ferrone , Federica and Danese , Vittoria and Cecchetti , Veronica and Pepe , Jessica and Cipriani , Cristiana and Colangelo , Luciano**. Controversies Surrounding Vitamin D: Focus on Supplementation and Cancer. International Journal of Environmental Research and Public Health (20190111) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[3] **Bilezikian , John P. and Formenti , Anna Maria and Adler , Robert A. and Binkley , Neil and Bouillon , Roger and Lazaretti-Castro , Marise and Marcocci , Claudio and Napoli , Nicola and Rizzoli , Rene and Giustina , Andrea**. Vitamin D: Dosing, levels, form, and route of administration: Does one approach fit all? Reviews in Endocrine and Metabolic Disorders (2021-Dec-01) src:dx.doi.org. src:doi.org. src:link.springer.com.

[4] **Giustina , Andrea and Bouillon , Roger and Binkley , Neil and Sempos , Christopher and Adler , Robert A and Bollerslev , Jens and DawsonHughes , Bess and Ebeling , Peter R and Feldman , David and Heijboer , Annemieke and Jones , Glenville and Kovacs , Christopher S and LazarettiCastro , Marise and**

Lips , Paul and Marcocci , Claudio and Minisola , Salvatore and Napoli , Nicola and Rizzoli , Rene and Scragg , Robert and White , John H and Formenti , Anna Maria and Bilezikian , John P. Controversies in Vitamin D: A Statement From the Third International Conference JBMR Plus (11/10/2020) src:dx.doi.org. src:asbmr.onlinelibrary.wiley.com.

[5] **Amrein , Karin and Scherkl , Mario and Hoffmann , Magdalena and Neuwersch-Sommeregger , Stefan and Köstenberger , Markus and Tmava Berisha , Adelina and Martucci , Gennaro and Pilz , Stefan and Malle , Oliver**. Vitamin D deficiency 2.0: an update on the current status worldwide European Journal of Clinical Nutrition (2020) src:dx.doi.org. src:www.nature.com. src:www.nature.com.

[6] **Lai , Rai-Hua and Hsu , Chih-Cheng and Yu , Ben-Hui and Lo , Yu-Ru and Hsu , Yueh-Ying and Chen , Mei-Hsin and Juang , Jyh-Lyh**. Vitamin D supplementation worsens Alzheimer's progression: Animal model and human cohort studies Aging Cell (07/12/2022) src:dx.doi.org. src:onlinelibrary.wiley.com. src:onlinelibrary.wiley.com. src:onlinelibrary.wiley.com.

[7] **Kennel , Kurt A. and Drake , Matthew T. and Hurley , Daniel L.**. Vitamin D Deficiency in Adults: When to Test and How to Treat. Mayo Clinic Proceedings (2010-Aug) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[8] **Chris Kresser , M.S.**. Vitamin D: More Is Not Better Chris Kresser LLC (08/02/2016) src:chriskresser.com. src:chriskresser.com.

[9] **Cipriani , Cristiana and Pepe , Jessica and Colangelo , Luciano and Minisola , Salvatore**. Vitamin D and Secondary Hyperparathyroid States. Frontiers of hormone research (20180329) src:dx.doi.org. src:pubmed.ncbi.nlm.nih.gov.

[10] **Pietrzyk , Robert A and Jones , Jeffrey A and Sams , Clarence F and Whitson , Peggy A**. Renal stone formation among astronauts. Aviation, space, and environmental medicine (2007-Apr) src:pubmed.ncbi.nlm.nih.gov.

[11] **Felsenfeld , Arnold J and Levine , Barton S**. Calcitonin, the forgotten hormone: does it deserve to be forgotten? Clinical kidney journal (20150320) src:dx.doi.org. src:pubmed.ncbi.nlm.nih.gov.

[12] **Tisman , Glenn and Garcia , April**. Control of prostate cancer associated with withdrawal of a supplement containing folic acid, L-methyltetrahydrofolate and vitamin B12: a case report Journal of Medical Case Reports (08/25/2011) src:dx.doi.org. src:jmedicalcasereports.biomedcentral.com.

[13] **Rendina , Domenico and De Filippo , Gianpaolo and Iannuzzo , Gabriella and Abate , Veronica and Strazzullo , Pasquale and Falchetti , Alberto**. Idiopathic Osteoporosis and Nephrolithiasis: Two Sides of the Same Coin? International Journal of Molecular Sciences (20201031) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[14] **Martina , Vavrusova, and André C. , Garcia, and Bente P. , Danielsen, and Leif H. , Skibsted,**. Spontaneous supersaturation of calcium citrate from simultaneous isothermal dissolution of sodium citrate and sparingly soluble calcium hydroxycarboxylates in water RSC Adv. (2017) src:dx.doi.org. src:pubs.rsc.org.

[15] **Abrams , S.A.**. Vitamin D in Preterm and Full-Term Infants Ann Nutr Metab (2020) src:dx.doi.org. src:www.karger.com. src:www.karger.com.

[16] **Barbarawi , Mahmoud and Kheiri , Babikir and Zayed , Yazan and Barbarawi , Owais and Dhillon , Harsukh and Swaid , Bakr and Yelangi , Anitha and Sundus , Saira and Bachuwa , Ghassan and Alkotob , Mohammad Luay and Manson , JoAnn E.**. Vitamin D Supplementation and Cardiovascular Disease Risks in More Than 83000 Individuals in 21 Randomized Clinical Trials JAMA Cardiology 765 (08/01/2019) src:dx.doi.org. src:jamanetwork.com.

[17] **Nudy , Matthew and Krakowski , George and Ghahramani , Mehrdad and Ruzieh , Mohammed and Foy , Andrew J.**. Vitamin D supplementation, cardiac events and stroke: A systematic review and meta-regression analysis IJC Heart & Vasculature (2020) src:dx.doi.org. src:www.sciencedirect.com.

[18] **Momosaki , Ryo and Abo , Masahiro and Urashima , Mitsuyoshi**. Vitamin D Supplementation and Post-Stroke Rehabilitation: A Randomized, Double-Blind, Placebo-Controlled Trial. Nutrients (20190607) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[19] **Selim , Fayrouz O. and Fahmi , Rasha M. and Ali , Ayman E. and Raafat , Nermin and Elsaid , Ahmed F.**. Serum vitamin D levels in acute stroke patients The Egyptian Journal of Neurology, Psychiatry and Neurosurgery (2019) src:dx.doi.org. src:ejnpn.springeropen.com.

[20] **Berghout , Brian P. and Fani , Lana and Heshmatollah , Alis and Koudstaal , Peter J. and Ikram , M. Arfan and Zillikens , M. Carola and Ikram , M. Kamran**. Vitamin D Status and Risk of Stroke Stroke (2019) src:dx.doi.org. src:www.ahajournals.org.

[21] **Tsilidis , Konstantinos K and Heath , Alicia K and Agnoli , Claudia and Krogh , Vittorio and de Boer , Ian H and Kobylecki , Camilla Jannie and Çolak , Yunus and Zittermann , Armin and Sundström , Johan and Welsh , Paul and Weiderpass , Elisabete and Aglago , Elom K and Ferrari , Pietro and Clarke , Robert and Boutron , Marie-Christine and Severi , Gianluca and MacDonald , Conor and Providencia , Rui and Masala , Giovanna and Ros , Raul Zamora and Boer , Jolanda and Verschuren , WM Monique and Cawthon , Peggy and Schierbeck , Louise L and Cooper , Cyrus and Schulze , Matthias B and Bergmann , Manuela M and Hannemann , Anke and Kiechl , Stefan and Brenner , Hermann and van Schoor , Natasja M and Albertorio , Juan R and Sacerdote , Carlotta and Linneberg , Allan and Kaarhus , Line L and Huerta , José María and Imaz , Liher and Joergensen , Christel and Ben-Shlomo , Yoav and Lundqvist , Annamari and Gallacher , John and Sattar , Naveed and Wood , Angela M and Wareham , Nicholas J and Nordestgaard , Borge G and Angelantonio , Emanuele Di and Danesh , John and Butterworth , Adam S and Burgess , Stephen and Sofianopoulou , Eleni and Kaptoge , Stephen K and Afzal , Shoaib and Jiang , Tao and Gill , Dipender and Gundersen , Thomas E and Bolton , Thomas R and Allara , Elias and**

Arnold , Matthew G and Mason , Amy M and Chung , Ryan and M Pennells , Lisa A and Shi , Fanchao and Sun , Luanluan and Willeit , Peter and Forouhi , Nita G and Langenberg , Claudia and Sharp , Stephen J and Panico , Salvatore and Engström , Gunnar and Melander , Olle and N Tong , Tammy Y and Perez-Cornago , Aurora and Norberg , Margareta and Johansson , Ingegerd and Katzke , Verena and Srour , Bernard and Sánchez , María José and Redondo-Sánchez , Daniel and Olsen , Anja and Dahm , Christina C and Overvad , Kim and Brustad , Magritt and Skeie , Guri and Moreno-Iribas , Conchi and Onland-Moret , N Charlotte and van der Schouw , Yvonne T. Estimating dose-response relationships for vitamin D with coronary heart disease, stroke, and all-cause mortality: observational and Mendelian randomisation analyses The Lancet Diabetes & Endocrinology 837-846 (2021) src:dx.doi.org. src:www.thelancet.com.

[22] **Larsson , Susanna C and Orsini , Nicola and Wolk , Alicja**. Dietary calcium intake and risk of stroke: a dose-response meta-analysis The American Journal of Clinical Nutrition (2013-04) src:dx.doi.org. src:doi.org. src:academic.oup.com. src:academic.oup.com.

[23] **Bellinge , Jamie W. and Dalgaard , Frederik and Murray , Kevin and Connolly , Emma and Blekkenhorst , Lauren C. and Bondonno , Catherine P. and Lewis , Joshua R. and Sim , Marc and Croft , Kevin D. and Gislason , Gunnar and TorpPedersen , Christian and Tjonneland , Anne and Overvad , Kim and Hodgson , Jonathan M. and Schultz , Carl and Bondonno , Nicola P.**. Vitamin K Intake and Atherosclerotic Cardiovascular Disease in the Danish Diet Cancer and Health Study Journal of the American Heart Association (2021) src:dx.doi.org. src:www.ahajournals.org. src:www.ahajournals.org. src:www.ahajournals.org.

[24] **M.J. Marchywka**. A Proposed Qualitative Non-monotonic Paradox Resolving Actvitiy-Coagulability Curve for Vitamin K (June 1, 2021) src:www.researchgate.net.

[25] **M.J. Marchywka**. Supplement Usage Including Vitamin K by a Heartworm Positive Pregnant Pit Bull and Her Puppies (September 29, 2021) src:www.researchgate.net.

[26] **Zhang , Dongdong and Cheng , Cheng and Wang , Yan and Sun , Hualei and Yu , Songcheng and Xue , Yuan and Liu , Yiming and Li , Wenjie and Li , Xing**. Effect of Vitamin D on Blood Pressure and Hypertension in the General Population: An Update Meta-Analysis of Cohort Studies and Randomized Controlled Trials Preventing Chronic Disease (01/09/2020) src:dx.doi.org. src:www.cdc.gov.

[27] **Pilz , Stefan and Gaksch , Martin and Kienreich , Katharina and Grübler , Martin and Verheyen , Nicolas and Fahrleitner-Pammer , Astrid and Treiber , Gerlies and Drechsler , Christiane and Hartaigh , Bríain ó and Obermayer-Pietsch , Barbara and Schwetz , Verena and Aberer , Felix and Mader , Julia and Scharnagl , Hubert and Meinitzer , Andreas and Lerchbaum , Elisabeth and Dekker , Jacqueline M. and Zittermann , Armin and März , Winfried and Tomaschitz , Andreas**. Effects of Vitamin D on Blood Pressure and Cardiovascular Risk Factors Hypertension (2015) src:dx.doi.org. src:www.ahajournals.org. src:www.ahajournals.org. src:www.ahajournals.org.

[28] **Legarth , Christian and Grimm , Daniela and Wehland , Markus and Bauer , Johann and Krüger , Marcus**. The Impact of Vitamin D in the Treatment of Essential Hypertension International Journal of Molecular Sciences 455 (02/03/2018) src:dx.doi.org. src:www.mdpi.com.

[29] **He , Silu and Hao , Xiyuan**. The effect of vitamin D3 on blood pressure in people with vitamin D deficiency: A system review and meta-analysis. Medicine (20190513) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[30] **Smith , Megan B and May , Heidi T and Blair , Tami L and Anderson , Jeffrey L and Muhlestein , Joseph B and Horne , Benjamin D and Lappe , Donald L and Day , John D and Crandall , Brian G and Weiss , Peter and Osborn , Jeffrey S and Bunch , Thomas J**. Abstract 14699: Vitamin D Excess Is Significantly Associated with Risk of Atrial Fibrillation Circulation (2011) src:dx.doi.org. src:www.ahajournals.org. src:www.ahajournals.org. src:www.ahajournals.org.

[31] **Huang , Wei-ling and Yang , Jun and Yang , Jian and Wang , Hui-bo and Yang , Chao-jun and Yang , Ying**. Vitamin D and new-onset atrial fibrillation: A meta-analysis of randomized controlled trials Hellenic Journal of Cardiology (2018) src:dx.doi.org. src:www.sciencedirect.com.

[32] **Chetty , Vasudevan V. and Chetty , Manoranjenni**. Potential benefit of vitamin D supplementation in people with respiratory illnesses, during the COVID19 pandemic Clinical and Translational Science 2111-2116 (2021) src:dx.doi.org. src:ascpt.onlinelibrary.wiley.com.

[33] **Cho , Herim and Myung , Seung-Kwon and Cho , Hae-Eun**. Efficacy of Vitamin D Supplements in Treatment of Acute Respiratory Infection: A Meta-analysis for Randomized Controlled Trials. Nutrients (20220308) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[34] **Kumar , Jogender and Kumar , Prawin and Goyal , Jagdish Prasad and Thakur , Chirag and Choudhary , Puja and Meena , Jitendra and Charan , Jaykaran and Singh , Kuldeep and Gupta , Atul**. Vitamin D supplementation in childhood asthma: a systematic review and meta-analysis of randomised controlled trials ERJ Open Research (2022) src:dx.doi.org. src:openres.ersjournals.com. src:openres.ersjournals.com.

[35] **Jolliffe , David A. and Holt , Hayley and Greenig , Matthew and Talaei , Mohammad and Perdek , Natalia and Pfeffer , Paul and Maltby , Sheena and Symons , Jane and Barlow , Nicola L. and Normandale , Alexa and Garcha , Rajvinder and Richter , Alex G. and Faustini , Sian E. and Orton , Christopher and Ford , David and Lyons , Ronan A. and Davies , Gwyneth A. and Kee , Frank and Griffiths , Christopher J. and Norrie , John and Sheikh , Aziz and Shaheen , Seif O. and Relton , Clare and Martineau , Adrian R.**. Vitamin D Supplements for Prevention of Covid-19 or other Acute Respiratory Infections: a Phase 3 Randomized Controlled Trial (CORONAVIT) medRxiv (2022) src:dx.doi.org. src:www.medrxiv.org. src:www.medrxiv.org. src:www.medrxiv.org.

[36] **Villasis-Keever , Miguel A and Lpez-Alarcn , Mardia G and Miranda-Novales , Guadalupe and Zurita-Cruz , Jessie N and Barrada-Vzquez , Aly S and Gonzlez-Ibarra , Joaqun and Martnez-Reyes , Monserrat and Grajales-Muiz , Concepcin and Santacruz-Tinoco , Clara E and Martnez-Miguel , Bernardo and Maldonado-Hernndez , Jorge and Cifuentes-Gonzlez , Yazmn and Klnder-Klnder , Miguel and Garduo-Espinosa , Juan and Lpez-Martnez , Briseida and Parra-Ortega , Israel**. Efficacy and Safety of Vitamin D Supplementation to Prevent COVID-19 in Frontline Healthcare Workers. A Randomized Clinical Trial. Archives of Medical Research (20220418) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[37] **Hosseini , Banafsheh and El Abd , Asmae and Ducharme , Francine M**. Effects of Vitamin D Supplementation on COVID-19 Related Outcomes: A Systematic Review and Meta-Analysis. Nutrients (20220520) src:dx.doi.org. src:pubmed.ncbi.nlm.nih.gov.

[38] **Varikasuvu , Seshadri Reddy and Thangappazham , Balachandar and Vykunta , Alekya and Duggina , Pragathi and Manne , Munikumar and Raj , Hemanth and Aloori , Sowjanya**. COVID-19 and vitamin D (Co-VIVID study): a systematic review and meta-analysis of randomized controlled trials Expert Review of Anti-infective Therapy 907-913 (02/03/2022) src:dx.doi.org. src:www.tandfonline.com.

[39] **Beran , Azizullah and Mhanna , Mohammed and Srour , Omar and Ayesh , Hazem and Stewart , Jamie M. and Hjouj , Majdal and Khokher , Waleed and Mhanna , Asmaa S. and Ghazaleh , Dana and Khader , Yasmin and Sayeh , Wasef and Assaly , Ragheb**. Clinical significance of micronutrient supplements in patients with coronavirus disease 2019: A comprehensive systematic review and meta-analysis Clinical Nutrition ESPEN 167-177 (2022) src:dx.doi.org. src:clinicalnutritionespen.com.

[40] **Mariani Javier AND Antonietti Laura AND Tajer Carlos AND Ferder León AND Inserra Felipe AND Sanchez Cunto Milagro AND Brosio Diego AND Ross Fernando AND Zylberman Marcelo AND López Daniel Emilio AND Luna Hisano Cecilia AND Maristany Batisda Sebastián AND Pace Gabriela AND Salvatore Adrián AND Hogrefe Jimena Fernanda AND Turela Marcela AND Gaido Andrés AND Rodera Beatriz AND Banega Elizabeth AND Iglesias María Eugenia AND Rzepeski Mariela AND Gomez Portillo Juan Manuel AND Bertelli Magalí AND Vilela Andrés AND Heffner Leandro AND Annetta Verónica Laura AND Moracho Lucila AND Carmona Maximiliano AND Melito Graciela AND Martínez María José AND Luna Gloria AND Vensentini Natalia AND Manucha , Walter**. High-dose vitamin D versus placebo to prevent complications in COVID-19 patients: Multicentre randomized controlled clinical trial PLOS ONE (2022-05) src:dx.doi.org. src:doi.org. src:journals.plos.org.

[41] **Bolland , Mark J and Avenell , Alison and Grey , Andrew and Gamble , Greg**. Vitamin D and acute respiratory infection: secondary analysis of a previous randomised controlled trial and updated meta-analyses medRxiv (2022) src:dx.doi.org. src:www.medrxiv.org. src:www.medrxiv.org. src:www.medrxiv.org.

[42] **Marcinkowska , Ewa and Brown , Geoffrey**. Editorial: Vitamin D and COVID-19: New Mechanistic and Therapeutic Insights Frontiers in Pharmacology (2022) src:dx.doi.org. src:www.frontiersin.org. src:www.frontiersin.org.

[43] **Thacher , Tom D.**. Evaluating the Evidence in Clinical Studies of Vitamin D in COVID-19. Nutrients (20220121) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[44] **Karonova , Tatiana L. and Golovatyuk , Ksenia A. and Kudryavtsev , Igor V. and Chernikova , Alena T. and Mikhaylova , Arina A. and Aquino , Arthur D. and Lagutina , Daria I. and Zaikova , Ekaterina K. and Kalinina , Olga V. and Golovkin , Alexey S. and Grant , William B. and Shlyakhto , Evgeny V.**. Effect of Cholecalciferol Supplementation on the Clinical Features and Inflammatory Markers in Hospitalized COVID-19 Patients: A Randomized, Open-Label, Single-Center Study Nutrients 2602 (06/23/2022) src:dx.doi.org. src:www.mdpi.com.

[45] **Quinn , Emma K and Fenton , Shelby and Ford-Sahibzada , Chelsea A and Harper , Andrew and Marcon , Alessandro R and Caulfield , Timothy and Fazel , Sajjad S and Peters , Cheryl E**. COVID-19 and Vitamin D Misinformation on YouTube: Content Analysis JMIR Infodemiology e32452 (03/14/2022) src:dx.doi.org. src:infodemiology.jmir.org.

[46] **Hahn , Jill and Cook , Nancy R and Alexander , Erik K and Friedman , Sonia and Walter , Joseph and Bubes , Vadim and Kotler , Gregory and Lee , I-Min and Manson , JoAnn E and Costenbader , Karen H**. Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial BMJ e066452 (01/26/2022) src:dx.doi.org. src:www.bmj.com.

[47] **Chandler , Paulette D. and Chen , Wendy Y. and Ajala , Oluremi N. and Hazra , Aditi and Cook , Nancy and Bubes , Vadim and Lee , I-Min and Giovannucci , Edward L. and Willett , Walter and Buring , Julie E. and Manson , JoAnn E.**. Effect of Vitamin D¡sub¿3¡/sub¿ Supplements on Development of Advanced Cancer JAMA Network Open e2025850 (11/18/2020) src:dx.doi.org. src:jamanetwork.com.

[48] **Keum , N. and Chen , Q-Y. and Lee , D. H. and Manson , J. E. and Giovannucci , E.**. Vitamin D supplementation and total cancer incidence and mortality by daily vs. infrequent large-bolus dosing strategies: a meta-analysis of randomised controlled trials British Journal of Cancer (06/08/2022) src:dx.doi.org. src:www.nature.com. src:www.nature.com.

[49] **Manson , JoAnn E. and Cook , Nancy R. and Lee , I-Min and Christen , William and Bassuk , Shari S. and Mora , Samia and Gibson , Heike and Gordon , David and Copeland , Trisha and D'Agostino , Denise and Friedenberg , Georgina and Ridge , Claire and Bubes , Vadim and Giovannucci , Edward L. and Willett , Walter C. and Buring , Julie E.**. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease New England Journal of Medicine (2019) src:dx.doi.org. src:doi.org. src:www.nejm.org.

[50] **Li, WJ and Chen, KH and Huang, LW and Tsai, YL and Seow, KM**. Low Maternal Serum 25Ux2010Hydroxyvitamin D Concentration Is Associated With Postpartum Hemorrhage: A Retrospective Observational Study. Frontiers

in Endocrinology (2022) src:www.ncbi.nlm.nih.gov.

[51] **Bischoff-Ferrari , Heike A. and Willett , Walter C. and Manson , JoAnn E. and Dawson-Hughes , Bess and Manz , Markus G. and Theiler , Robert and Braendle , Kilian and Vellas , Bruno and Rizzoli , René and Kressig , Reto W. and Staehelin , Hannes B. and Da Silva , José P. and Armbrecht , Gabriele and Egli , Andreas and Kanis , John A. and Orav , Endel J. and Gaengler , Stephanie**. Combined Vitamin D, Omega-3 Fatty Acids, and a Simple Home Exercise Program May Reduce Cancer Risk Among Active Adults Aged 70 and Older: A Randomized Clinical Trial Frontiers in Aging (2022) src:dx.doi.org. src:www.frontiersin.org. src:www.frontiersin.org.

[52] **Nakamura , Satoshi and Sato , Yuiko and Kobayashi , Tami and Kaneko , Yosuke and Ito , Eri and Soma , Tomoya and Okada , Hiroyuki and Miyamoto , Kana and Oya , Akihito and Matsumoto , Morio and Nakamura , Masaya and Kanaji , Arihiko and Miyamoto , Takeshi**. Vitamin D protects against immobilization-induced muscle atrophy via neural crest-derived cells in mice Scientific Reports (07/22/2020) src:dx.doi.org. src:www.nature.com. src:www.nature.com.

[53] **Rondanelli , Mariangela and Klersy , Catherine and Terracol , Gilles and Talluri , Jacopo and Maugeri , Roberto and Guido , Davide and Faliva , Milena A and Solerte , Bruno S and Fioravanti , Marisa and Lukaski , Henry and Perna , Simone**. Whey protein, amino acids, and vitamin D supplementation with physical activity increases fat-free mass and strength, functionality, and quality of life and decreases inflammation in sarcopenic elderly The American Journal of Clinical Nutrition (2016-02) src:dx.doi.org. src:doi.org. src:academic.oup.com. src:academic.oup.com.

[54] **LeBoff , M. S. and Greenspan , S. L. and Insogna , K. L. and Lewiecki , E. M. and Saag , K. G. and Singer , A. J. and Siris , E. S.**. The clinician's guide to prevention and treatment of osteoporosis Osteoporosis International (2022-Apr-28) src:dx.doi.org. src:doi.org. src:link.springer.com.

[55] **Burt , Lauren A. and Billington , Emma O. and Rose , Marianne S. and Raymond , Duncan A. and Hanley , David A. and Boyd , Steven K.**. Effect of High-Dose Vitamin D Supplementation on Volumetric Bone Density and Bone Strength JAMA 736 (08/27/2019) src:dx.doi.org. src:jamanetwork.com.

[56] **Cheung Angela M AND Tile Lianne AND Lee Yuna AND Tomlinson George AND Hawker Gillian AND Scher Judy AND Hu Hanxian AND Vieth Reinhold AND Thompson Lilian AND Jamal Sophie AND Josse , Robert**. Vitamin K Supplementation in Postmenopausal Women with Osteopenia (ECKO Trial): A Randomized Controlled Trial PLOS Medicine (2008-10) src:dx.doi.org. src:doi.org. src:journals.plos.org.

[57] **Carson , Dennis A.**. An infectious origin of extraskeletal calcification. Proceedings of the National Academy of Sciences of the United States of America (1998-Jul-7) src:www.ncbi.nlm.nih.gov.

[58] **da Silva , Alexandre Ferreira**. Differential diagnosis of pathological intracranial calcifications in patients with microcephaly related to congenital Zika virus infection. Radiologia Brasileira (2018-Jul-Aug) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[59] **Jones , E. L. and Cameron , A. H.**. Pulmonary calcification in viral pneumonia Journal of Clinical Pathology (1969) src:dx.doi.org. src:jcp.bmj.com. src:jcp.bmj.com. src:jcp.bmj.com.

[60] **Rea , Gaetano and Costigliola , Adriano and Calabrese , Cecilia**. A storm of stones in the lungs: an uncommon sequela of varicella pneumonia. Jornal Brasileiro de Pneumologia (2017-May-Jun) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[61] **Soares , Bruno P. and Provenzale , James M.**. Imaging of Herpesvirus Infections of the CNS American Journal of Roentgenology 39-48 (2016) src:dx.doi.org. src:www.ajronline.org.

[62] **Wang , Jeffrey and Zhou , Jimmy J. and Robertson , Graham R. and Lee , Vincent W.**. Vitamin D in Vascular Calcification: A Double-Edged Sword? Nutrients (20180522) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[63] **Keasey , M. P. and Lemos , R. R. and Hagg , T. and Oliveira , J. M.**. Vitamin-D receptor agonist calcitriol reduces calcification in vitro through selective upregulation of SLC20A2 but not SLC20A1 or XPR1 Scientific Reports (05/17/2016) src:dx.doi.org. src:www.nature.com. src:www.nature.com.

[64] **Price , P A and Williamson , M K and Sloper , S A**. 1,25-Dihydroxyvitamin D3 increases citrate secretion from osteosarcoma cells. Journal of Biological Chemistry 2537-2540 (1984) src:dx.doi.org. src:www.jbc.org.

[65] **Bell , Taison D. and Demay , Marie B. and Burnett-Bowie , Sherri-Ann M.**. The Biology and Pathology of Vitamin D Control in Bone. Journal of cellular biochemistry (2010-Sep-1) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[66] **Nguyen-Yamamoto , Loan and Tanaka , Ken-Ichiro and St-Arnaud , Rene and Goltzman , David**. Vitamin D-regulated osteocytic sclerostin and BMP2 modulate uremic extraskeletal calcification JCI Insight (07/11/2019) src:dx.doi.org. src:insight.jci.org.

[67] **Hari Kumar , K. V. S. and Shijith , K. P. and Ahmad , F. M. H.**. Bell's palsy at high altitude – an unsuspected finding Military Medical Research (05/12/2016) src:dx.doi.org. src:mmrjournal.biomedcentral.com.

[68] **Nollet , Lukas and Van Gils , Matthias and Verschuere , Shana and Vanakker , Olivier**. The Role of Vitamin K and Its Related Compounds in Mendelian and Acquired Ectopic Mineralization Disorders. International Journal of Molecular Sciences (20190430) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[69] **Tesfamariam , Belay**. Involvement of Vitamin K-Dependent Proteins in Vascular Calcification Journal of Cardiovascular Pharmacology and Therapeutics 323-333 (03/24/2019) src:dx.doi.org. src:journals.sagepub.com.

[70] **Schurgers , Leon J and Spronk , Henri H and Soute , Berry M and Schiffers , Paul M and DeMey , Jo R and Vermeer , Cees**. Regression of warfarin-induced medial elastocalcinosis by high intake of vitamin K in rats. Blood (2007-Apr-1) src:dx.doi.org. src:pubmed.ncbi.nlm.nih.gov.

[71] **Malihi , Zarintaj and Wu , Zhenqiang and Stewart , Alistair W and Lawes , Carlene MM and Scragg , Robert**. Hypercalcemia, hypercalciuria, and kidney stones in long-term studies of vitamin D supplementation: a systematic review and meta-analysis The American Journal of Clinical Nutrition (2016-09) src:dx.doi.org. src:doi.org. src:academic.oup.com. src:academic.oup.com.

[72] **Baron , John A. and Barry , Elizabeth L. and Mott , Leila A. and Rees , Judy R. and Sandler , Robert S. and Snover , Dale C. and Bostick , Roberd M. and Ivanova , Anastasia and Cole , Bernard F. and Ahnen , Dennis J. and Beck , Gerald J. and Bresalier , Robert S. and Burke , Carol A. and Church , Timothy R. and Cruz-Correa , Marcia and Figueiredo , Jane C. and Goodman , Michael and Kim , Adam S. and Robertson , Douglas J. and Rothstein , Richard and Shaukat , Aasma and Seabrook , March E. and Summers , Robert W.**. A Trial of Calcium and Vitamin D for the Prevention of Colorectal Adenomas New England Journal of Medicine (2015) src:dx.doi.org. src:doi.org. src:www.nejm.org.

[73] **Sunyecz , John A**. The use of calcium and vitamin D in the management of osteoporosis. Therapeutics and Clinical Risk Management (200808) src:www.ncbi.nlm.nih.gov.

[74] **Xiao , Yunfei and Yin , Shan and Bai , Yunjin and Wang , Jiahao and Cui , Jianwei and Wang , Jia**. Association between urine cobalt and prevalence of kidney stones in Americans aged $\geq$ 20 years old Environmental Science and Pollution Research (07/26/2022) src:dx.doi.org. src:pubmed.ncbi.nlm.nih.gov.

[75] **Bargagli , Matteo and Ferraro , Pietro Manuel and Vittori , Matteo and Lombardi , Gianmarco and Gambaro , Giovanni and Somani , Bhaskar**. Calcium and Vitamin D Supplementation and Their Association with Kidney Stone Disease: A Narrative Review Nutrients 4363 (12/04/2021) src:dx.doi.org. src:www.mdpi.com.

[76] **Park , Clara Yongjoo**. Vitamin D in the Prevention and Treatment of Osteoarthritis: From Clinical Interventions to Cellular Evidence. Nutrients (20190122) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[77] **Konstari , S and Paananen , M and Heliövaara , M and Knekt , P and Marniemi , J and Impivaara , O and Arokoski , J and Karppinen , J**. Association of 25-hydroxyvitamin D with the incidence of knee and hip osteoarthritis: a 22-year follow-up study Scandinavian Journal of Rheumatology (2012) src:dx.doi.org. src:doi.org. src:www.tandfonline.com.

[78] **Li , Hui and Zeng , Chao and Wei , Jie and Yang , Tuo and Gao , Shu-Guang and Li , Yu-Sheng and Luo , Wei and Xiao , Wen-Feng and Xiong , Yi-Lin and Lei , Guang-Hua**. Serum Calcium Concentration Is Inversely Associated With Radiographic Knee Osteoarthritis: A Cross-Sectional Study. Medicine (20160212) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[79] **Stücker , Sina and Bollmann , Miriam and Garbers , Christoph and Bertrand , Jessica**. The role of calcium crystals and their effect on osteoarthritis pathogenesis Best Practice & Research Clinical Rheumatology (2021) src:dx.doi.org. src:www.sciencedirect.com. src:www.sciencedirect.com.

[80] **Jung , Youn-Kwan and Han , Min-Su and Park , Hye-Ri and Lee , Eun-Ju and Jang , Ji-Ae and Kim , Gun-Woo and Lee , Sun-Young and Moon , DaeWon and Han , Seungwoo**. Calcium-phosphate complex increased during subchondral bone remodeling affects earlystage osteoarthritis Scientific Reports (01/11/2018) src:dx.doi.org. src:www.nature.com. src:www.nature.com.

[81] **Hunter , D. J. and Hart , D. and Snieder , H. and Bettica , P. and Swaminathan , R. and Spector , T. D.**. Evidence of altered bone turnover, vitamin D and calcium regulation with knee osteoarthritis in female twins Rheumatology (2003-11) src:dx.doi.org. src:doi.org. src:academic.oup.com. src:academic.oup.com.

[82] **Palacios , Cristina and Kostiuk , Lia K and Peña-Rosas , Juan Pablo**. Vitamin D supplementation for women during pregnancy Cochrane Database of Systematic Reviews (07/26/2019) src:dx.doi.org. src:www.cochrane.org.

[83] **Scalise , Mariafrancesca and Galluccio , Michele and Console , Lara and Pochini , Lorena and Indiveri , Cesare**. The Human SLC7A5 (LAT1): The Intriguing Histidine/Large Neutral Amino Acid Transporter and Its Relevance to Human Health. Frontiers in Chemistry (20180622) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[84] **Jia , Xiaotong and Cao , Yang and Ye , Lingyu and Liu , Xueqing and Huang , Yujia and Yuan , Xiaolei and Lu , Chunmei and Xu , Jie and Zhu , Hui**. Vitamin D stimulates placental L-type amino acid transporter 1 (LAT1) in preeclampsia Scientific Reports (03/17/2022) src:dx.doi.org. src:www.nature.com. src:www.nature.com.

[85] **Sass , Laerke and Vinding , Rebecca Kofod and Stokholm , Jakob and Bjarnadóttir , Elín and Noergaard , Sarah and Thorsen , Jonathan and Sunde , Rikke Bjersand and McGrath , John and Bonnelykke , Klaus and Chawes , Bo and Bisgaard , Hans**. High-Dose Vitamin D Supplementation in Pregnancy and Neurodevelopment in Childhood JAMA Network Open e2026018 (12/08/2020) src:dx.doi.org. src:jamanetwork.com.

[86] **Karras , S. N. and Anagnostis , P. and Naughton , D. and Annweiler , C. and Petroczi , A. and Goulis , D. G.**. Vitamin D during pregnancy: why observational studies suggest deficiency and interventional studies show no... 'Springer Science and Business Media LLC' /[pdfId] (12/01/2015) src:dx.doi.org. src:core.ac.uk.

[87] **Bouillon , Roger and Carmeliet , Geert and Verlinden , Lieve and van Etten , Evelyne and Verstuyf , Annemieke and Luderer , Hilary F. and Lieben , Liesbet and Mathieu , Chantal and Demay , Marie**. Vitamin D and Human Health: Lessons from Vitamin D Receptor Null Mice. Endocrine Reviews (20080811) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[88] **Demay , Marie B.**. Physiological Insights from the Vitamin D receptor knockout mouse. Calcified tissue international (20120818) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[89] **Shi , Yongyan and Liu , Ziyun and Cui , Xuewei and Zhao , Qun and Liu , Tianjing**. Intestinal vitamin D receptor knockout protects from oxazolone-induced colitis Cell Death & Disease (06/15/2020) src:dx.doi.org. src:www.nature.com. src:www.nature.com.

[90] **Wikimedia projects , Contributors to**. Vitamin D Wikipedia (07/02/2022) src:en.wikipedia.org. src:en.wikipedia.org.

[91] **Autier , Philippe**. Vitamin D Supplementation and Total Mortality<subtitle>A Meta-analysis of Randomized Controlled Trials</subtitle> Archives of Internal Medicine 1730 (16) src:dx.doi.org. src:jamanetwork.com.

[92] **Acharya , Prakash and Dalia , Tarun and Ranka , Sagar and Sethi , Prince and Oni , Olurinde A and Safarova , Maya S and Parashara , Deepak and Gupta , Kamal and Barua , Rajat S**. The Effects of Vitamin D Supplementation and 25-Hydroxyvitamin D Levels on the Risk of Myocardial Infarction and Mortality Journal of the Endocrine Society (2021-07) src:dx.doi.org. src:doi.org. src:academic.oup.com. src:academic.oup.com.

[93] **Pilz , Stefan and Trummer , Christian and Theiler-Schwetz , Verena and Grübler , Martin R. and Verheyen , Nicolas D. and Odler , Balazs and Karras , Spyridon N. and Zittermann , Armin and März , Winfried**. Critical Appraisal of Large Vitamin D Randomized Controlled Trials Nutrients 303 (2) src:dx.doi.org. src:www.mdpi.com.

[94] **Dai , Lei and Liu , Man and Chen , Liangkai**. Association of Serum 25-Hydroxyvitamin D Concentrations With All-Cause and Cause-Specific Mortality Among Adult Patients With Existing Cardiovascular Disease Frontiers in Nutrition (2021) src:dx.doi.org. src:www.frontiersin.org. src:www.frontiersin.org.

[95] **Melamed , M. L. and Michos , E. D. and Post , W. and Astor , B.**. 25-Hydroxyvitamin D Levels and the Risk of Mortality in the General Population Archives of Internal Medicine 1629-1637 (15) src:dx.doi.org. src:jamanetwork.com.

[96] **van der Schouw , Yvonne T and Tsilidis , Konstantinos K and Heath , Alicia K and Agnoli , Claudia and Krogh , Vittorio and de Boer , Ian H and Kobylecki , Camilla Jannie and Çolak , Yunus and Zittermann , Armin and Sundström , Johan and Welsh , Paul and Weiderpass , Elisabete and Aglago , Elom K and Ferrari , Pietro and Clarke , Robert and Boutron , Marie-Christine and Severi , Gianluca and MacDonald , Conor and Providencia , Rui and Masala , Giovanna and Ros , Raul Zamora and Boer , Jolanda and Verschuren , WM Monique and Cawthon , Peggy and Schierbeck , Louise L and Cooper , Cyrus and Schulze , Matthias B and Bergmann , Manuela M and Hannemann , Anke and Kiechl , Stefan and Brenner , Hermann and van Schoor , Natasja M and Albertorio , Juan R and Sacerdote , Carlotta and Linneberg , Allan and Kaarhus , Line L and Huerta , José María and Imaz , Liher and Joergensen , Christel and Ben-Shlomo , Yoav and Lundqvist , Annamari and Gallacher , John and Sattar , Naveed and Wood , Angela M and Wareham , Nicholas J and Nordestgaard , Borge G and Angelantonio , Emanuele Di and Danesh , John and Butterworth , Adam S and Burgess , Stephen and Sofianopoulou , Eleni and Kaptoge , Stephen K and Afzal , Shoaib and Jiang , Tao and Gill , Dipender and Gundersen , Thomas E and Bolton , Thomas R and Allara , Elias and Arnold , Matthew G and Mason , Amy M and Chung , Ryan and M Pennells , Lisa A and Shi , Fanchao and Sun , Luanluan and Willeit , Peter and Forouhi , Nita G and Langenberg , Claudia and Sharp , Stephen J and Panico , Salvatore and Engström , Gunnar and Melander , Olle and N Tong , Tammy Y and Perez-Cornago , Aurora and Norberg , Margareta and Johansson , Ingegerd and Katzke , Verena and Srour , Bernard and Sánchez , María José and Redondo-Sánchez , Daniel and Olsen , Anja and Dahm , Christina C and Overvad , Kim and Brustad , Magritt and Skeie , Guri and Moreno-Iribas , Conchi and Onland-Moret , N Charlotte**. Estimating dose-response relationships for vitamin D with coronary heart disease, stroke, and all-cause mortality: observational and Mendelian randomisation analyses The Lancet Diabetes & Endocrinology 837-846 (12) src:dx.doi.org. src:www.thelancet.com.

[97] **Grant , William B. and Anouti , Fatme Al and Boucher , Barbara J. and Dursun , Erdinç and Gezen-Ak , Duygu and Jude , Edward B. and Karonova , Tatiana and Pludowski , Pawel**. A Narrative Review of the Evidence for Variations in Serum 25-Hydroxyvitamin D Concentration Thresholds for Optimal Health Nutrients 639 (02/02/2022) src:dx.doi.org. src:www.mdpi.com.

[98] **Chan , Yap-Hang and Schooling , C. Mary and Zhao , Jie V. and Yeung , Shiu-Lun Au and Hai , Jo Jo and Thomas , G. Neil and Cheng , Kar-Keung and Jiang , Chao-Qiang and Wong , Yuen-Kwun and Au , Ka-Wing and Tang , Clara S. and Cheung , Chloe Y. and Xu , Aimin and Sham , Pak-Chung and Lam , Tai-Hing and Lam , Karen Siu-Ling and Tse , Hung-Fat**. Mendelian randomization analysis of vitamin D in the secondary prevention of hypertensive-diabetic subjects: role of facilitating blood pressure control Genes & Nutrition (2022-Jan-29) src:dx.doi.org. src:doi.org. src:link.springer.com.

[99] **Wikimedia projects , Contributors to**. Inverse problem Wikipedia (05/17/2022) src:en.wikipedia.org.

[100] **Povaliaeva , Alexandra and Bogdanov , Viktor and Pigarova , Ekaterina and Dzeranova , Larisa and Katamadze , Nino and Malysheva , Natalya and Ioutsi , Vitaliy and Nikankina , Larisa and Rozhinskaya , Liudmila and Mokrysheva , Natalia**. Impaired Vitamin D Metabolism in Hospitalized COVID-19 Patients Pharmaceuticals 906 (07/22/2022) src:dx.doi.org. src:www.mdpi.com.

[101] **Owens , Daniel J. and Allison , Richard and Close , Graeme L.**. Vitamin D and the Athlete: Current Perspectives and New Challenges Sports Medicine (2018-Mar-01) src:dx.doi.org. src:doi.org. src:link.springer.com.

[102] **Bikle , Daniel D.**. Vitamin D: Production, Metabolism and Mechanisms of Action MDText.com, Inc. (12/31/2021) src:www.ncbi.nlm.nih.gov. src:www.ncbi.nlm.nih.gov.

[103] **Khundmiri , Syed Jalal and Murray , Rebecca D. and Lederer , Eleanor**. PTH and Vitamin D Comprehensive Physiology 561-601 (03/15/2016) src:dx.doi.org. src:onlinelibrary.wiley.com.

[104] **Mike J Marchywka**. Missing the B0AT1 : Amino Acid Malnutrition in Aging and SARS-CoV2 (January 3, 2022) src:www.researchgate.net. src:www.academia.edu.

[105] **Lavelli , Vera and DIncecco , Paolo and Pellegrino , Luisa**. Vitamin D Incorporation in Foods: Formulation Strategies, Stability, and Bioaccessibility as Affected by the Food Matrix. Foods (20210825) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[106] **Boyko , Nikolay and Zhilyakova , Elena and Malyutina , Anastasiya and Novikov , Oleg and Pisarev , Dmitriy and Abramovich , Rimma and Potanina , Olga and Lazar , Simon and Mizina , Praskovia and Sahaidak-Nikitiuk , Rita**. Studying and Modeling of the Extraction Properties of the Natural Deep Eutectic Solvent and Sorbitol-Based Solvents in Regard to Biologically Active Substances from Glycyrrhizae Roots. Molecules (20200325) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[107] **Mike J Marchywka**. Happy Again : Possible Canine Riboflavin Deficiency (March 27, 2022) src:www.researchgate.net. src:www.academia.edu. src:zenodo.org. src:www.linkedin.com.

[108] **Mike J Marchywka**. Experiences with a Family of Science Based Kitchen Snacks for Dogs (January 2, 2022) src:www.researchgate.net. src:www.academia.edu. src:www.linkedin.com.

[109] **Genah , Shirley and Monici , Monica and Morbidelli , Lucia**. The Effect of Space Travel on Bone Metabolism: Considerations on Today's Major Challenges and Advances in Pharmacology International Journal of Molecular Sciences 4585 (04/27/2021) src:dx.doi.org.

[110] **Goodenow-Messman , Debra A. and Gokoglu , Suleyman A. and Kassemi , Mohammad and Myers , Jerry G.**. Numerical characterization of astronaut CaOx renal stone incidence rates to quantify in-flight and post-flight relative risk npj Microgravity (01/28/2022) src:dx.doi.org. src:www.nature.com. src:www.nature.com.

[111] **Enrico , Catalano**. Nutraceutical and Nutrients Development for Space Travel Springer International Publishing (2022) src:dx.doi.org. src:doi.org. src:link.springer.com.

[112] **Stepaniak , Philip C. and Ramchandani , Suneil R. and Jones , Jeffrey A.**. Acute Urinary Retention Among Astronauts Aerospace Medical Association (-) src:www.ingentaconnect.com.

[113] **Sakhaee , Khashayar and Poindexter , John and Aguirre , Crystal**. The Effects of Bariatric Surgery on Bone and Nephrolithiasis. Bone (20151208) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[114] **Gasmi , Amin and Bjørklund , Geir and Mujawdiya , Pavan Kumar and Semenova , Yuliya and Peana , Massimiliano and Dosa , Alexandru and Piscopo , Salva and Gasmi Benahmed , Asma and Costea , Daniel Ovidiu**. Micronutrients deficiences in patients after bariatric surgery European Journal of Nutrition (2022-Feb-01) src:dx.doi.org. src:doi.org. src:link.springer.com.

[115] **Chen , Chien-Hua and Lin , Cheng-Li and Jeng , Long-Bin**. Association between chronic pancreatitis and urolithiasis: A population-based cohort study. PLoS ONE (20180309) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[116] **Medicine , Institute of**. Dietary Reference Intakes for Calcium and Vitamin D The National Academies Press (2011) src:dx.doi.org. src:nap.nationalacademies.org.

[117] **Heer , Martina**. Nutritional interventions related to bone turnover in European space missions and simulation models Nutrition (2002) src:dx.doi.org. src:www.sciencedirect.com. src:www.sciencedirect.com.

[118] **Iwamoto , Jun and Takeda , Tsuyoshi and Sato , Yoshihiro**. Interventions to prevent bone loss in astronauts during space flight. The Keio journal of medicine (2005-Jun) src:dx.doi.org. src:pubmed.ncbi.nlm.nih.gov.

[119] **Tang , Hong and Rising , Hope Hui and Majji , Manoranjan and Brown , Robert D.**. Long-Term Space Nutrition: A Scoping Review Nutrients 194 (12/31/2021) src:dx.doi.org. src:www.mdpi.com.

[120] **Schwaderer , Andrew L and Oduguwa , Abimbola and Kusumi , Kirsten**. Urinary stone disease in pediatric and adult metabolic bone clinic patients. Urolithiasis (20170308) src:dx.doi.org. src:pubmed.ncbi.nlm.nih.gov.

[121] **Qin , Lei and He , Tailin and Yang , Dazhi and Wang , Yishu and Li , Zhenjian and Yan , Qinnan and Zhang , Peijun and Chen , Zecai and Lin , Sixiong and Gao , Huanqing and Yao , Qing and Xu , Zhen and Tang , Bin and Yi , Weihong and Xiao , Guozhi**. Osteocyte upbeta1 integrin loss causes low bone mass and impairs bone mechanotransduction in mice Journal of Orthopaedic Translation (2022) src:dx.doi.org. src:www.sciencedirect.com.

[122] **Schepelmann , Martin and Ranieri , Marianna and Lopez-Fernandez , Irene and Webberley , Thomas S. and Brennan , Sarah C. and Yarova , Polina L. and Graca , Joao and Hanif , Umar-Khetaab and Müller , Christian and Manhardt , Teresa and Salzmann , Martina and Quasnichka , Helen and Price , Sally A. and Ward , Donald T. and Gilbert , Thierry and Matchkov , Vladimir V. and Fenton , Robert A. and Herberger , Amanda and Hwong , Jenna and Santa Maria , Christian and Tu , Chia-Ling and Kallay , Enikö and Valenti , Giovanna and Chang , Wenhan and Riccardi , Daniela**. Impaired Mineral Ion Metabolism in a Mouse Model of Targeted Calcium-Sensing Receptor (CaSR) Deletion from Vascular Smooth Muscle Cells Journal of the American Society of Nephrology (2022) src:dx.doi.org. src:jasn.asnjournals.org. src:jasn.asnjournals.org. src:jasn.asnjournals.org.

[123] **Gu , Ke and Liu , Guangmang and Wu , Caimei and Jia , Gang and Zhao , Hua and Chen , Xiaoling and Tian , Gang and Cai , Jingyi and Zhang , Ruinan and Wang , Jing**. Tryptophan improves porcine intestinal epithelial cell restitution through the CaSR/Rac1/PLC-upgamma1 signaling pathway Food & Function 8787-8799 (09/20/2021) src:dx.doi.org. src:pubs.rsc.org.

[124] **Ouyang , Liu and Yu , Changjiang and Xie , Zhiyong and Su , Xiaoyan and Xu , Zengmei and Song , Ping and Li , Jian and Huang , Hui and Ding , Ye and Zou , Ming-Hui**. Indoleamine 2,3-Dioxygenase 1 Deletion–Mediated Kynurenine Insufficiency in Vascular Smooth Muscle Cells Exacerbates Arterial Calcification Circulation (2022) src:dx.doi.org. src:www.ahajournals.org. src:www.ahajournals.org.

[125] **M.J. Marchywka**. On the age distribution of SARS-Cov-2 Patients (July 1, 2020) src:www.linkedin.com.

[126] **M.J. Marchywka**. On the age distribution of SARS-Cov-2 Patients (March 12, 2021) src:www.researchgate.net.

[127] **Schafer , Anne L and Weaver , Connie M and Black , Dennis M and Wheeler , Amber L and Chang , Hanling and Szefc , Gina V and Stewart , Lygia and Rogers , Stanley J and Carter , Jonathan T and Posselt , Andrew M and Shoback , Dolores M and Sellmeyer , Deborah E**. Intestinal Calcium Absorption Decreases Dramatically After Gastric Bypass Surgery Despite Optimization of Vitamin D Status Journal of Bone and Mineral Research 1377-1385 (05/21/2015) src:dx.doi.org. src:asbmr.onlinelibrary.wiley.com.

[128] **Shan , Jin-Hua and Bai , Xiao-Juan and Han , Lu-Lu and Yuan , Yuan and Sun , Xue-Feng**. Changes with aging in gastric biomarkers levels and in biochemical factors associated with Helicobacter pylori infection in asymptomatic Chinese population. World Journal of Gastroenterology (20170828) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[129] **Ben-Porat , Tair and Elazary , Ram and Sherf-Dagan , Shiri and Goldenshluger , Ariela and Brodie , Ronit and Mintz , Yoav and Weiss , Ram**. Bone Health following Bariatric Surgery: Implications for Management Strategies to Attenuate Bone Loss Advances in Nutrition 114-127 (2018-04-11-2018-03-01) src:dx.doi.org. src:watermark.silverchair.com.

[130] **Bhatti , Umer Hasan and Duffy , Andrew J. and Roberts , Kurt Eric and Shariff , Amir Hafeez**. Nephrolithiasis after bariatric surgery: A review of pathophysiologic mechanisms and procedural risk International Journal of Surgery (2016) src:dx.doi.org. src:www.sciencedirect.com.

[131] **Weiss , Daniel**. Long-term Complications of Bariatric Surgery JAMA 186 (01/12/2021) src:dx.doi.org. src:jamanetwork.com.

[132] **Knight , John and Easter , Linda H. and Neiberg , Rebecca and Assimos , Dean G. and Holmes , Ross P.**. Increased protein intake on controlled oxalate diets does not increase urinary oxalate excretion. Urological research (20090129) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[133] **Huang , Y. and Zhang , Y.H. and Chi , Z.P. and Huang , R. and Huang , H. and Liu , G. and Zhang , Y. and Yang , H. and Lin , J. and Yang , T. and Cao , S.Z.**. The Handling of Oxalate in the Body and the Origin of Oxalate in Calcium Oxalate Stones Urol Int (2020) src:dx.doi.org. src:www.karger.com. src:www.karger.com.

[134] **VIETH , REINHOLD**. How to Optimize Vitamin D Supplementation to Prevent Cancer, Based on Cellular Adaptation and Hydroxylase Enzymology Anticancer Research (2009) src:ar.iiarjournals.org. src:ar.iiarjournals.org. src:ar.iiarjournals.org.

[135] **Mawer , E. Barbara and Backhouse , Joan and Holman , Carlene A. and Lumb , G. A. and Stanbury , S. W.**. The Distribution and Storage of Vitamin D and its Metabolites in Human Tissues Clinical Science 413-431 (09/01/1972) src:dx.doi.org. src:watermark.silverchair.com.

[136] **Jones , K. S. and Assar , S. and Harnpanich , D. and Bouillon , R. and Lambrechts , D. and Prentice , A. and Schoenmakers , I.**. 25(OH)D2 Half-Life Is Shorter Than 25(OH)D3 Half-Life and Is Influenced by DBP Concentration and Genotype. The Journal of Clinical Endocrinology and Metabolism (20140602) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[137] **Jones , Glenville**. Pharmacokinetics of vitamin D toxicity The American Journal of Clinical Nutrition (2008-08) src:dx.doi.org. src:doi.org. src:academic.oup.com. src:academic.oup.com.

[138] **Carrelli , Angela and Bucovsky , Mariana and Horst , Ronald and Cremers , Serge and Zhang , Chengchen and Bessler , Marc and Schrope , Beth and Evanko , John and Blanco , Jody and Silverberg , Shonni J and Stein , Emily M**. Vitamin D Storage in Adipose Tissue of Obese and Normal Weight Women Journal of Bone and Mineral Research 237-242 (10/24/2016) src:dx.doi.org. src:asbmr.onlinelibrary.wiley.com.

[139] **Walsh , James Bernard and McCartney , Daniel M. and Laird , Éamon and McCarroll , Kevin and Byrne , Declan G. and Healy , Martin and O'Shea , Paula M. and Kenny , Rose Anne and Faul , John L.**. Title: Understanding a Low Vitamin D State in the Context of COVID-19 Frontiers in Pharmacology (2022) src:dx.doi.org. src:www.frontiersin.org. src:www.frontiersin.org.

[140] **LeBlanc , A and Schneider , V and Spector , E and Evans , H and Rowe , R and Lane , H and Demers , L and Lipton , A**. Calcium absorption, endogenous excretion, and endocrine changes during and after long-term bed rest. Bone (1995-Apr) src:dx.doi.org. src:pubmed.ncbi.nlm.nih.gov.

[141] **Tsai , Syun-Hui and Tseng , Yu-Hwei and Chiou , Wen-Fei and Chen , Shih-Ming and Chung , Yi and Wei , Wen-Chi and Huang , Wen-Ching**. The Effects of Whole-Body Vibration Exercise Combined With an Isocaloric High-Fructose Diet on Osteoporosis and Immunomodulation in Ovariectomized Mice. Frontiers in nutrition (20220620) src:dx.doi.org. src:pubmed.ncbi.nlm.nih.gov.

[142] **Granchi , Donatella and Baldini , Nicola and Ulivieri , Fabio Massimo and Caudarella , Renata**. Role of Citrate in Pathophysiology and Medical Management of Bone Diseases. Nutrients (20191025) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[143] **Consiglio Marco AND Destefanis Michele AND Morena Deborah AND Foglizzo Valentina AND Forneris Mattia AND Pescarmona Gianpiero AND Silvagno , Francesca**. The Vitamin D Receptor Inhibits the Respiratory Chain, Contributing to the Metabolic Switch that Is Essential for Cancer Cell Proliferation PLOS ONE (2015-12) src:dx.doi.org. src:doi.org. src:journals.plos.org.

[144] **Boer , Willem and Fivez , Tom and Laenen , Margot Vander and Bruckers , Liesbeth and Grön , Hans Jurgen and Schetz , Miet and Straaten , Heleen Oudemans-van**. Citrate dose for continuous hemofiltration: effect on calcium and magnesium balance, parathormone and vitamin D status, a randomized controlled trial BMC Nephrology (2021) src:dx.doi.org. src:bmcnephrol.biomedcentral.com.

[145] **Costello , Leslie C and Franklin , Renty B**. Plasma Citrate Homeostasis: How It Is Regulated; And Its Physiological and Clinical Implications. An Important, But Neglected, Relationship in Medicine. HSOA journal of human endocrinology

(20161231) src:www.ncbi.nlm.nih.gov.

[146] **Mike J Marchywka**. Wetting Tryptophan With Calcium Pantothenate (December 4, 2021) src:www.researchgate.net. src:www.academia.edu. src:www.linkedin.com.

[147] **Coperchini , F and Greco , A and Denegri , M and Ripepi , F A and Grillini , B and Bertini , J and Cali , B and Villani , L and Magri , F and Croce , L and Gaetano , C and Cappelli , C and Trimboli , P and Chiovato , L and Rotondi , M**. Vitamin D and interferon-gamma co-operate to increase the ACE-2 receptor expression in primary cultures of human thyroid cells. Journal of endocrinological investigation (20220712) src:dx.doi.org. src:pubmed.ncbi.nlm.nih.gov.

[148] **Rajendra , Akhil and Mishra , Ajay Kumar and Francis , Nirmal Raj and Carey , Ronald Benton**. Severe hypercalcemia in a patient with pulmonary tuberculosis. Journal of Family Medicine and Primary Care (2016-Apr-Jun) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[149] **Masterjohn , Christopher**. Vitamin D toxicity redefined: vitamin K and the molecular mechanism. Medical hypotheses (20061204) src:dx.doi.org. src:pubmed.ncbi.nlm.nih.gov.

[150] **O'Connor , Eibhlis and Molgaard , Christian and Michaelsen , Kim F and Jakobsen , Jette and Cashman , Kevin D**. Vitamin D-vitamin K interaction: effect of vitamin D supplementation on serum percentage undercarboxylated osteocalcin, a sensitive measure of vitamin K status, in Danish girls. The British journal of nutrition (20100521) src:dx.doi.org. src:pubmed.ncbi.nlm.nih.gov.

[151] **Campbell , H. E. and Escudier , M. P. and Patel , P. and Challacombe , S. J. and Sanderson , J. D. and Lomer , M. C. E.**. Review article: cinnamon- and benzoate-free diet as a primary treatment for orofacial granulomatosis Alimentary Pharmacology & Therapeutics 687-701 (08/04/2011) src:dx.doi.org. src:onlinelibrary.wiley.com.

[152] . DR. WILEY AND BENZOATE OF SODA Journal of the American Medical Association 562 (02/13/1909) src:dx.doi.org. src:jamanetwork.com.

[153] . Scientific Opinion on the reevaluation of benzoic acid (E 210), sodium benzoate (E 211), potassium benzoate (E 212) and calcium benzoate (E 213) as food additives EFSA Journal (-) src:dx.doi.org. src:efsa.onlinelibrary.wiley.com.

[154] **Alqahtani , Mohammed S. and Kazi , Mohsin and Alsenaidy , Mohammad A. and Ahmad , Muhammad Z.**. Advances in Oral Drug Delivery Frontiers in Pharmacology (2021) src:dx.doi.org. src:www.frontiersin.org. src:www.frontiersin.org.

[155] **Muldowney , F P and Freaney , R and Barnes , E**. Dietary chloride and urinary calcium in stone disease. QJM : monthly journal of the Association of Physicians (1994-Aug) src:pubmed.ncbi.nlm.nih.gov.

[156] **Queau , Yann and Bijsmans , Esther S. and Feugier , Alexandre and Biourge , Vincent C.**. Increasing dietary sodium chloride promotes urine dilution and decreases struvite and calcium oxalate relative supersaturation in healthy dogs and cats Journal of Animal Physiology and Animal Nutrition 1524-1530 (03/10/2020) src:dx.doi.org. src:onlinelibrary.wiley.com.

[157] **Rodgers , Allen and Gauvin , Daniel and Edeh , Samuel and Allie-Hamdulay , Shameez and Jackson , Graham and Lieske , John C.**. Sulfate but Not Thiosulfate Reduces Calculated and Measured Urinary Ionized Calcium and Supersaturation: Implications for the Treatment of Calcium Renal Stones. PLoS ONE (20140725) src:dx.doi.org. src:www.ncbi.nlm.nih.gov.

[158] . Interdisciplinary Nutritional Management and Care for Older Adults Perspectives in Nursing Management and Care for Older Adults (2021) src:dx.doi.org. src:library.oapen.org.

[159] **Nelson , Adam J. and Raggi , Paolo and Wolf , Myles and Gold , Alexander M. and Chertow , Glenn M. and Roe , Matthew T.**. Targeting Vascular Calcification in Chronic Kidney Disease JACC: Basic to Translational Science (2020) src:dx.doi.org. src:www.jacc.org.

[160] **Turner , Mandy E. and Holden , Rachel M.**. Risks of Vitamin K Antagonism Arteriosclerosis, Thrombosis, and Vascular Biology (2020) src:dx.doi.org. src:www.ahajournals.org.

[161] **DalCanto , Elisa and Beulens , Joline J and Elders , Petra and Rutters , Femke and Stehouwer , Coen A and vanderHeijden , Amber A and vanBallegooijen , Adriana J**. The Association of Vitamin D and Vitamin K Status with Subclinical Measures of Cardiovascular Health and All-Cause Mortality in Older Adults: The Hoorn Study The Journal of Nutrition (2020-10) src:dx.doi.org. src:doi.org. src:academic.oup.com. src:academic.oup.com.

[162] **Diederichsen , Axel C.P. and Lindholt , Jes S. and Möller , Sören and Ovrehus , Kristian A. and Auscher , Soren and Lambrechtsen , Jess and Hosbond , Susanne E. and Alan , Dilek H. and Urbonaviciene , Grazina and Becker , Soren W. and Fredgart , Maise H. and Hasific , Selma and Folkestad , Lars and Gerke , Oke and Rasmussen , Lars Melholt and Moller , Jacob E. and Mickley , Hans and Dahl , Jordi S.**. Vitamin K2 and D in Patients With Aortic Valve Calcification: A Randomized Double-Blinded Clinical Trial Circulation (2022) src:dx.doi.org. src:www.ahajournals.org. src:www.ahajournals.org. src:www.ahajournals.org.

[163] **Xian , Joshua Zhaojun and Lu , Mimi and Fong , Felicia and Qiao , Rong and Patel , Nikhil Rajesh and Abeydeera , Dishan and Iriana , Sidney and Demer , Linda L. and Tintut , Yin**. Statin Effects on Vascular Calcification Arteriosclerosis, Thrombosis, and Vascular Biology (2021) src:dx.doi.org. src:www.ahajournals.org.

[164] **Ikegami , Yuichi and Inoue , Ikuo and Inoue , Kaiji and Shinoda , Yuichi and Iida , Shinichiro and Goto , Seiichi and Nakano , Takanari and Shimada , Akira and Noda , Mistuhiko**. The annual rate of coronary artery calcification with combination therapy with a PCSK9 inhibitor and a statin is lower than that with statin monotherapy npj Aging and Mechanisms of Disease (06/22/2018) src:dx.doi.org. src:www.nature.com. src:www.nature.com.

[165] **ZhelyazkovaSavova , Maria D. and Yotov , Yoto T. and Nikolova , Miglena N. and NazifovaTasinova , Neshe F. and Vankova , Deyana G. and Atanasov , Atanas A. and Galunska , Bistra Tz.**. Statins, vascular calcification, and vitamin Kdependent proteins: Is there a relation? The Kaohsiung Journal of Medical Sciences 624-631

(02/26/2021) src:dx.doi.org. src:onlinelibrary.wiley.com.

[166] **Okuyama , Harumi and Langsjoen , Peter H and Hamazaki , Tomohito and Ogushi , Yoichi and Hama , Rokuro and Kobayashi , Tetsuyuki and Uchino , Hajime**. Statins stimulate atherosclerosis and heart failure: pharmacological mechanisms Expert Review of Clinical Pharmacology (2015) src:dx.doi.org. src:doi.org. src:www.tandfonline.com.

[167] **De Vriese , An S. and Caluwé , Rogier and Pyfferoen , Lotte and De Bacquer , Dirk and De Boeck , Koen and Delanote , Joost and De Surgeloose , Didier and Van Hoenacker , Piet and Van Vlem , Bruno and Verbeke , Francis**. Multicenter Randomized Controlled Trial of Vitamin K Antagonist Replacement by Rivaroxaban with or without Vitamin K2 in Hemodialysis Patients with Atrial Fibrillation: the Valkyrie Study Journal of the American Society of Nephrology (2020) src:dx.doi.org. src:jasn.asnjournals.org. src:jasn.asnjournals.org.

[168] **Chan , Kevin E. and Lazarus , J. Michael and Thadhani , Ravi and Hakim , Raymond M.**. Anticoagulant and Antiplatelet Usage Associates with Mortality among Hemodialysis Patients Journal of the American Society of Nephrology (2009) src:dx.doi.org. src:jasn.asnjournals.org. src:jasn.asnjournals.org.

[169] **David S. , Mathiesen, and Asger , Lund, and Tina , Vilsboll, and Filip K. , Knop, and Jonatan I. , Bagger,**. Amylin and Calcitonin: Potential Therapeutic Strategies to Reduce Body Weight and Liver Fat Frontiers in Endocrinology (2021) src:dx.doi.org. src:www.frontiersin.org. src:www.frontiersin.org.

[170] **OLSON BURDETTE E. , JR. and DELUCA , HECTOR F. and POTTS JOHN T. , JR.**. Calcitonin Inhibition of Vitamin D-Induced Intestinal Calcium Absorption Endocrinology (1972-01) src:dx.doi.org. src:doi.org. src:academic.oup.com. src:academic.oup.com.

[171] **Mike J Marchywka**. Update to Covid-19 Age Distribution Notes (August 17, 2021) src:www.researchgate.net.

[172] **Neubauer , Emilie-Fleur and Poole , Angela Z and Neubauer , Philipp and Detournay , Olivier and Tan , Kenneth and Davy , Simon K and Weis , Virginia M**. A diverse host thrombospondin-type-1 repeat protein repertoire promotes symbiont colonization during establishment of cnidarian-dinoflagellate symbiosis eLife (2017-may) src:dx.doi.org. src:doi.org. src:elifesciences.org.

[173] **Shcherbakova , Aleksandra and Preller , Matthias and Taft , Manuel H and Pujols , Jordi and Ventura , Salvador and Tiemann , Birgit and Buettner , Falk FR and Bakker , Hans**. C-mannosylation supports folding and enhances stability of thrombospondin repeats eLife (2019-dec) src:dx.doi.org. src:doi.org. src:elifesciences.org.

[174] **Rubio , Angela and Ghosh , Sanjay and Mülleder , Michael and Ralser , Markus and Mata , Juan**. Ribosome profiling reveals ribosome stalling on tryptophan codons and ribosome queuing upon oxidative stress in fission yeast Nucleic Acids Research (2020-12) src:dx.doi.org. src:doi.org. src:academic.oup.com. src:academic.oup.com.

[175] **Sonntag , J. and Vogel , M. and Geserick , M. and Eckelt , F. and Krner , A. and Raue , F. and Kiess , W. and Kratzsch , J.**. Age-Related Association of Calcitonin with Parameters of Anthropometry, Bone and Calcium Metabolism during Childhood Horm Res Paediatr (2020) src:dx.doi.org. src:www.karger.com. src:www.karger.com.

[176] **Mirjana Babic Leko and Nikolina Pleic and Ivana Gunjaca and Tatijana Zemunik**. Environmental Factors That Affect Parathyroid Hormone and Calcitonin Levels International Journal of Molecular Sciences 44 (12/21/2021) src:dx.doi.org. src:www.mdpi.com.

[177] **Bevilacqua , Maurizio and Dominguez , Ligia J. and Righini , Velella and Valdes , Valeria and Toscano , Rosanna and Sangaletti , Ornella and Vago , Tarcisio and Baldi , Gabriella and Barrella , Massimo and Bianchi-Porro , Gabriele**. Increased Gastrin and Calcitonin Secretion after Oral Calcium or Peptones Administration in Patients with Hypercalciuria: A Clue to an Alteration in Calcium-Sensing Receptor Activity The Journal of Clinical Endocrinology & Metabolism (2005-03) src:dx.doi.org. src:doi.org. src:academic.oup.com. src:academic.oup.com.

[178] **Monteiro , Fanny M. and Bach , Lennart T. and Brownlee , Colin and Bown , Paul and Rickaby , Rosalind E. M. and Poulton , Alex J. and Tyrrell , Toby and Beaufort , Luc and Dutkiewicz , Stephanie and Gibbs , Samantha and Gutowska , Magdalena A. and Lee , Renee and Riebesell , Ulf and Young , Jeremy and Ridgwell , Andy**. Why marine phytoplankton calcify Science Advances (-) src:dx.doi.org. src:www.science.org.

[179] **Cohen , Liat and Dean , Mason and Shipov , Anna and Atkins , Ayelet and Monsonego-Ornan , Efrat and Shahar , Ron**. Comparison of structural, architectural and mechanical aspects of cellular and acellular bone in two teleost fish Journal of Experimental Biology 1983-1993 (06/01/2012) src:dx.doi.org. src:journals.biologists.com.

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1. Pubmed eutils facilities and the basic research it provides.

2. Free software including Linux, R, LaTex etc.

3. Thanks everyone who contributed incidental support.

Appendix A: Statement of Conflicts

No specific funding was used in this effort and there are no relationships with others that could create a conflict of interest. I would like to develop these ideas further and have obvious bias towards making them appear successful. Barbara Cade, the dog owner, has worked in the pet food industry but this does not likely create a conflict. We have no interest in the makers of any of the products named in this work.

Appendix B: About the Authors and Facility

This work was performed at a dog rescue run by Barbara Cade and housed in rural Georgia. The author of this report ,Mike Marchywka, has a background in electrical engineering and has done extensive research using free online literature sources. I hope to find additional people interested in critically examining the results and verify that they can be reproduced effectively to treat other dogs.

Appendix C: Symbols, Abbreviations and Colloquialisms

TERM	definition and meaning
BMD	
BMI	
CI	
CKD	
CORONAVIT	
CVD	
FDA	
GI	
HR	
ICU	
KO	
NOAEL	
OR	
PTH	
RCT	
RYGB	
UV	
VD	
VDR	
VITAL	

Appendix D: General caveats and disclaimer

This document was created in the hope it will be interesting to someone including me by providing information about some topic that may include personal experience or a literature review or description of a speculative theory or idea. There is no assurance that the content of this work will be useful for any paricular purpose.

All statements in this document were true to the best of my knowledge at the time they were made and every attempt is made to assure they are not misleading or confusing. However, information provided by others and observations that can be manipulated by unknown causes ("gaslighting") may be misleading. Any use of this information should be preceded by validation including replication where feasible. Errors may enter into the final work at every step from conception and research to final editing.

Documents labelled "NOTES" or "not public" contain substantial informal or speculative content that may be terse and poorly edited or even sarcastic or profane. Documents labelled as "public" have generally been edited to be more coherent but probably have not been reviewed or proof read.

Generally non-public documents are labelled as such to avoid confusion and embarassment and should be read with that understanding.

Appendix E: Citing this as a tech report or white paper

Note: This is mostly manually entered and not assured to be error free.
This is tech report MJM-2022-010.

Version	Date	Comments
0.01	2022-05-21	Create from empty.tex template
0.80	2022-07-28	First release RFC/notes
-	July 28, 2022	version 0.80 MJM-2022-010
1.0	20xx-xx-xx	First revision for distribution

Released versions,
build script needs to include empty releases.tex

Version	Date	URL
0.80	2022-07-28	https://www.linkedin.com/posts/marchywka_review-of-issues-with-vitamin-d-hint-of-activity-6958364700
0.80	2022-07-28	https://www.researchgate.net/publication/362303875_Vitamin_D_Towards_A_Conflict_Resolving_Hypothesis
0.80	2022-07-28	https://www.academia.edu/s/999c2c3ee4
0.80	2022-07-28	https://zenodo.org/record/6922402#.YuJp3nXMJCU

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Supporting files. Note that some dates,sizes, and md5's will change as this is rebuilt.
This really needs to include the data analysis code but right now it is auto generated picking up things from prior build in many cases

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