

**Release Notes 2023-01-10 :** Fix bibliography from prior release otherwise no changes. 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 controversial 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 authors 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 viewpoints 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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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 work 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 nascent 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 equivocal 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 <sup>1</sup>.

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 remain 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." Vitamin 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, mobilizing 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 deposition [106]. The rest of this work outlines important considerations in asking better questions and getting more relevant data on interventions.

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<sup>1</sup> 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 <sup>2</sup> 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

<sup>2</sup> [https://www.nejm.org/doi/suppl/10.1056/NEJMoa1809944/suppl\\_file/nejmoa1809944\\_appendix.pdf](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 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 such 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 particular clinical result. However, D3 also increases citrate secretion from osteosarcoma cells [133] and details of experimental condition 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 herpesvirus is often associate with Bell’s Palsy and treatments are not always satisfactory due to “unclear pathogenesis” [58]. Herpesvirus 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 some models have failed to respond to vitamin K, it can reverse warfarin related calcifications 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 amino 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,

$$UV, diet \rightarrow D3 \rightarrow 25OHD \rightarrow 1, 25(OH)_2D \rightarrow VDR \quad (1)$$

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 effects 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 persist. 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<sup>3</sup> 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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<sup>3</sup> This may be a slight abuse of terminology as the question exists about "observed." I am using this for shorthand for " lowest dose to be worse than placebo " even if the damage is not observable without great effort.



**Thinking aloud**

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,

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

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

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

where  $r_0$  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

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

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

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

where  $d_c$  is some critical amount.

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

$$P(r; d) = A \exp(-(r - \langle r(d; r_0, b_1, c_1, b_2, c_2) \rangle)^2 / \sigma^2(d)) \quad (6)$$

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.

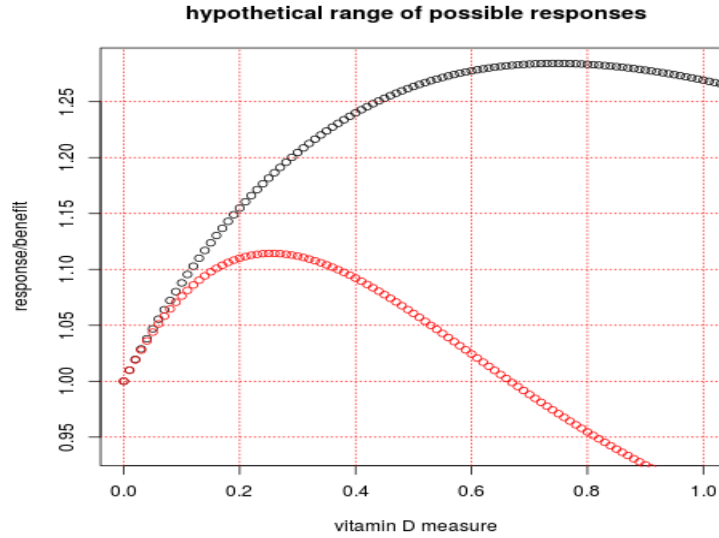


FIG. 1: Range of hypothesized responses to vitamin D for various patients. Note deleterious response at moderate doses ( red curve,  $c_2=b_2=1.5$  ) that benefit others ( black curve,  $c_2=b_2=.3$  ). Parameters common to both curves are  $r_0=b_1=c_1=1$ .

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 mechanotransduction 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 speculative 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 reduce 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 while 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<sup>4</sup> 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,

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

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

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

---

<sup>4</sup> 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  $\tau$  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-lives 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 <sup>5</sup> 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 informative as a comparator 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 lipophilic 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 thought 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 interpreted as somehow being therapeutic against SARS-Cov-2, it would

<sup>5</sup> 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 evaluated 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 statistics 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 often 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 chelators 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 inulin 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 in diet will ultimately 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 chloride . 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 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 calcification [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 calcitonin - 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 receptor peptides contain the "WxxWxxW" motif [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 significance 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 to 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 ectopic 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 from a molecule may not even be the dominant 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 distinguish distinct 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.

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### 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 particular 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 embarrassment 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
0.80x	2023-01-10	fix messed up bibliography
-	January 10, 2023	version 0.80x MJM-2022-010
1.0	20xx-xx-xx	First revision for distribution

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

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0.80	2022-07-28	<a href="https://www.researchgate.net/publication/362303875_Vitamin_D_Towards_A_Conflict_Resolving_Hypothesis">https://www.researchgate.net/publication/362303875_Vitamin_D_Towards_A_Conflict_Resolving_Hypothesis</a>
0.80	2022-07-28	<a href="https://www.academia.edu/s/999c2c3ee4">https://www.academia.edu/s/999c2c3ee4</a>
0.80	2022-07-28	<a href="https://zenodo.org/record/6922402#.YuJp3nXMJCU">https://zenodo.org/record/6922402#.YuJp3nXMJCU</a>

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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

```
3807 Jan 10 18:45 comment.cut ee545807b2a0e860c54d373083c91259
34971 Dec 28 11:35 /home/documents/latex/bib/mjm_tr.bib fbcabea2f3d21aa0800b8f7eaf7d4dfc
43410 Jan 10 17:42 /home/documents/latex/bib/releases.bib 31d2ad70c87d23816428dc79485d66c1
7331 Jan 24 2019 /home/documents/latex/pkg/fltpage.sty 73b3a2493ca297ef0d59d6c1b921684b
7434 Oct 21 1999 /home/documents/latex/pkg/lgrind.sty ea74beead1aa2b711ec2669ba60562c3
7162 Nov 13 2015 /home/documents/latex/pkg/mol2chemfig.sty f5a8b1719cee30a4df0739275ac75f8a
1069 Oct 15 2021 /home/documents/latex/share/includes/disclaimer-gaslight.tex 94142
b06063984d082bff3b400abe0fb
425 Oct 11 2020 /home/documents/latex/share/includes/disclaimer-status.tex b276f09e06a3a9114f927e4199f379f7
1478 May 14 2022 /home/documents/latex/share/includes/mjmaddbib.tex cb57cbf8cd5c5ac8f44c98b34ba9227a
```



```

122 Jun 27 2022 /home/documents/latex/share/includes/mjmlistings.tex 439aab9f9b760c03d4278a11e1a03079
4225 Oct 25 06:03 /home/documents/latex/share/includes/mycommands.tex 4c9a19e4d486f05addf05b60f79c3192
2901 Jun 17 2020 /home/documents/latex/share/includes/myskeletonpackages.tex
fcfd2e3c8d69d533932edaaa47f53a1
1538 Aug 14 2021 /home/documents/latex/share/includes/recent_template.tex 49763d2c29f74e4b54fa53b25c2cc439
940 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/amsfonts/cmextra/cmex7.tfm
f9e66c0105a30e64e3a0f5c4f79efb8d
852 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/amsfonts/symbols/msam10.tfm
b4a46d2c220ee4ffaaf87c608f8593cd
860 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/amsfonts/symbols/msam5.tfm
c4142ffef6136ff95621f9be99efb7cec
864 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/amsfonts/symbols/msam7.tfm 2998
d813a00ebf21070684f214a50f7e
844 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/amsfonts/symbols/msbm10.tfm
f7721eee07bdc9e743e6c5f3f7e3d06d
876 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/amsfonts/symbols/msbm5.tfm 9
e3df3efef7afc4b0381e88a6402f777
876 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/amsfonts/symbols/msbm7.tfm 374365713297
d597717720c5786882e5
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1056 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/cm/cmsy8.tfm 7ef80e56d3b9e223d3bce5a9065b95ad
36437 Jun 23 2022 keep/doserresponse.png 9705e12c7adac5b03cb7e8ecd33b8c7f
493512 Jul 27 14:42 non_pmc_vd.bib 6101ae1e76ef4c0fdb954efd76c8ab4f
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517 Jul 28 06:57 releases.tex b982bb61996c425ad0da5216c7700ecc
31050 Jul 21 2011 /usr/share/texlive/texmf-dist/bibtex/bst/urlbst/plainurl.bst
ffdaefb09013f5fd4b31e485c13933c1
1293990 Jul 23 2019 /var/lib/texmf/web2c/luatex/lualatex.fmt 0fdf3dce2c9cd956e421c2c52037b3cc
22711 Jan 10 18:45 vd.aux ba33b9564784493a6dc7a5a4f7290f70
93874 Jan 10 18:45 vd.bbl 54a8e1ee108076e3f2809a45df336163
627861 Jan 10 18:45 vd.bib 6bfab200b80c76f5671c482ea45b1cb1
3027 Jan 10 18:45 vd.blg cb5e87c77565f5a7757d52d137fafb02
4096 Jan 10 18:46 vd.bundle_checksums 794420681f54b369788ae2dbe5702f00
30630 Jan 10 18:45 vd.fls 8e237b5ff32155f4aaf35c043666be1b
3 Jan 10 18:45 vd.last_page 22cab69bca05d296a2d779a52cdee643
66530 Jan 10 18:45 vd.log 65c67d65d547cb9f1b08f8ff324ae4d1
1368 Jan 10 18:45 vd.out e5ce758524e03351379f4a3d878c9d6e
486829 Jan 10 18:45 vd.pdf c238cfbdc81a33d85962a45964096ec7
92294 Jan 10 18:45 vd.tex dfe72a6f4e8ce3faed204d9e3834bb81
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486829 Jan 10 18:45 vd.pdf c238cfbdc81a33d85962a45964096ec7

```