Release Note : This work describes an approach to covid-19 recognizing that severity in old age as an important clue to the disease process. Known and suspected disease processes are considered in terms of the literature on aging leading to a set of nutritional interventions that may effect both conditions. Initial personal experiences optimizing dog diets have demonstrated some encouraging results but organizing the literature has become an endless task. In the meantime, progress against covid-19 using conventional approaches appears to have reached a dead end. Strikingly absent from recent literature is any mention of vitamin K even when discussing TAM [120]. Tests of speculative ideas on aging may be easier and more productively performed against covid-19 so I dedided to release this early "notes" version as a basis for discussion. The more controversial ideas are mostly the result of re-evaluation of some old ideas in light of new findings. Continued literature searches seem to confirm the plausibility of the motivation but it is difficult to come up with a convincing argument for the more controversial issues without empirical trial and error. A goal of the work is to find simple informative and safe tests at this point. Two speculative ideas about SARS-Cov-2 and aging converged on leaking plasma membranes- that is, loss of tryptophan and high infidelity translation products that leak working with the action of NEDD4 on ACE2 to enhance viral entry in an attempt to regulate cytoplasmic ion concentrations. These ideas may not have merit but the similarities between conditions may have different reasons for existing while still pointing to same nutrients. This work should present enough information for the formulation of informative experiments to explore the ideas put forth.

On the age distribution of SARS-Cov-2 Patients

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The covid-19 disease caused by SARS-Cov-2 is ofen fatal, difficult to treat, and difficult to control without disruptive social actions such as distancing and lockdown which have detrimental effects of their own. The search for a better immediate solution has generated speculation on severity modulators among existing anti-viral and host directed approaches based on experience with similar diseases. One robust feature of the epidemic is a preference for older people leading to interest in informative theories of aging that may suggest virus mitigation strategies. SARS-Cov-2 is therefore a good test case for nascent theories on aging such as my ongoing work involving nutrient limitations. In normal aging, nutrient issues may be largely due to primary GI problems usually described as "asymptomatic" but reducing amino acid, cation, and fat soluble vitamin absorption. In the diseased state, host reactions place additional demands on existing nutrients while others may be programmatically destroyed suggesting that covid-19 patients with lower reserves will have worse outcomes. Many of the intervention ideas derived from my aging theory differ from conventional expectations but rely mostly on nutrient manipulation making them reasonably safe and easy for disriminating tests. Despite all the literture on SARS-Cov-2 some important gaps remain related to nutrient issues. ACE2 dynamics related to B0AT and NEDD4 seem to be ignored but are mentioned here. Coagulopathies are reported but neutrophil extracellular traps and protein C have been almost ignored . Protein C will be considered here while discussing a role for vitamin K.

The nutrient risks are both absolute deficiency and imbalance due to a prolonged disease oriented metabolism. I describe candidates for the most pathogenic virus related deficeincies among amino acids (tryptophan, tyrosine, and arginine), metals (mostly copper) and miscellaneous but critical nutrients such as vitamin K and citric acid.

Contents

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1. INTRODUCTION

The recently emerged coronavirus,SARS-Cov-2 , targets old people preferentially beyond what is seen in similar viral diseases [204] . While some SARS-Cov-2 related conditions have emerged targeting children [212] , their relation to the virus remains unclear. With no particularly promising cure in the known pipelines, it may be helpful to understand the characteristics of old age that lead to this distribution. In an ongoing work, I outline some characteristics of old age in dogs and humans analyzed as nutrient issues [141]. The features described in [141] generally relate to effective malnutrition that may cause the same age-related conditions that are prognostic for SARS-Cov-2 virulence with old age as a persistent predictor [226]. The nutrients highighted in [141] are known to the virology and immunology communities but roles may be unappreciated by conventional thinking. The different predictions regarding nutrient supplements make a good test of my theory and may help resolve some current limitations in progress against SARS-Cov-2 . Infectious disease provokes sudden loss of select nutrients, the aging theory addresses a more gradual loss of a wider range of nutrients at varying rates. So, different effects will be observed even if the causes are related and tests need to consider this among other factors. The effective malnutrition in both cases may not resemble classical forms such as food deprivation but that can be rationalized by the nature of the defects and their time evolution.

Several scientific publications have come out with nutritional approaches to covid-19 and many likely exist in other literature sources but none have been proven successful and none appear identical to this work. At least one group has come up with a dietary strategy for covid-19 but methodology and evaluation are unclear from the abstract[214] and there is also a more recent suggestion for a plant-based immunomodulatory diet[50] . One recent work discussed a link between aging and SARS-Cov-2 looking for pathways of interest, even mentioning mTOR [179], but did not apparently recommend the supplements suggested here. Nicotinamide or niacin supplementation was considered during an analysis of NAD fate in SARS-Cov-2 cases [81]. One work does specifically suggest copper for SARS-Cov-2 patients while warning about zinc [172] following some of the reasoning here but somewhat drawing on disinfectant properties and apparently not mentioning clotting issues and nutritional immunity. Another work describes a possible benefit from copper and N-acetylcysteine based on a literature search [10]. The present work is almost orthogonal to works such as [234] that promote vitamins D and E to the exclusion of those noted here. In fact, vitamin E is considered potnetially deleterious.

While metabolic changes in the disease state always make nutrition a concern, some recent reports should further motivate an interest in nutritional status for SARS-Cov-2 infected patients. One study of gene expression in bronchoalveolar lavage fluid from 3 groups of people demonstrated maximal down regulation of a group called " GPCR-Mediate Nutrient Sensing in Enteroendocrine Cells" in SARS-Cov-2 patients [237] (see for example [1]). Another report observed that ileal absorptive cells express ACE2 and appear receptive to infection [238] suggesting some sudden loss of nutrient uptake was possible. In common with other coronaviruses, SARS-Cov-2 uses ACE2 for entry but as ACE2 is also a chaperone for an amino acid transporter that transports tryptophan [230] anything that modulates its dynamics may relate to nutrient flow. Also specific to SARS-Cov-2 was the finding of unusual alterations in amino acid metabolism and down regulated platelet factor 4 along with lipid and steroid changes [196].

Currently, the SARS-Cov-2 literature does not address several specific features that may help discriminate among nutritional treatment candidates. In particular, absent is much about NEDD4 and ACE2 dynamics despite NEDD4's involvement in processes related to some prognostic conditions. NEDD4 senses intracellular ions and can internalize ACE2 [160] although the literature on SARS-Cov-2 [193] and earlier coronaviruses [217] does not mention it. As the endogeneous ligands may not provoke internalization (internalization in response to Angiotensin-II appears to be mediated by another receptor [39]) it is unclear if the virus itself can do that without help. NEDD4 is an attractive speculative explanation as it senses a common attribute of many predisposing conditions. A very recent comment mentions TAM and protein S but does not discuss vitamin K much [120]. Literature on protein C and the much of vitamin K dependent components are absent despite coagulopathies, the prognostic significance of protein C in ARDS [144] and the cutaneous manifestations possibly suggestive of their relevance. Nor is there much about NETs despite recurring issues with hyperactivavted neutrophils (or EET's and depleted eosinophils) and coagulopathies [145] and correspondingly no mention of a role for DNA-ase [240] [98] . In the absence of more information like this, or direct measures of local reduced vitamin K or tryptophan, empirically testing nutrient therapies may be worthwhile due to simplicity and informative value.

The work is organized a bit redundantly to make each section coherent but not complete in itself. The situations in disease and old age are outlined prior to a discussion of nurtrients they motivate for covid-19 management. Note that many of the steps in going from observations to logical interventions are empirical. The hypothezied details need

[1] https://targetexplorer.ingenuity.com/pathway/ING/ING:crzzc#!/api/rest/v1/client/searchPathwayNodes?pathwayId=ING:crzzc&rows=0&facetLimit=5000&responseType=default

not be entirely accurate for the approach to be informative and even effective.

2. SARS-COV-2 RELEVANT FEATURES, EPIDEMIOLOGY, POSSIBLE NUTRITIONAL INVOLVEMENT BASED ON SIMILAR DISEASES

2.1. General features

Generally studies have found increased severity or mortality in older people or younger people mostly with identifiable risk factors similar to diseases of old age. One work concluded that an age of 60 was a bad prognostic factor [129] One study of Japanese patients conclude various metrics were worst for people between 50-69 years old [150]. A recent CDC report broke down statistics by age and state showing hospitalizations per capita increasing with age from about 2 per 100,000 in the 18-49 group and almost 8 in the 50-64 approaching 17 for the oldest [61]. Conditions predisposing to severe disease include diabetes [102], cardiovascular diseases [23], hypertension and kidney disease [216]. Males may get more severe disease than females [191] and are generally known to have shorter life expectancies. Smoking is thought to reduce the risk leading to interest in nicotine [51] although physical barriers to infection may need to be considered.

Skin conditions have been variously described in the popular press as rashes or "covid toes". Some consider that urticaria with pyrexia may be a common early symptom [209]. Most reports link to Kawasaki disease (for example, [212]) This does not seem unique to SARS-Cov-2 as a novel coronavirus , New Haven coronavirus, was linked to Kawasaki Disease in 2005 [49]. While no obvious literature exists on vitamin K involvement, as discussed later there is reason to suspect it. It is interesting to note that SARS-CoV nsp10 interacts with NADH4L [125] which speculatively may allow it to mutate to interact with VKORC or other proteins with vaguely similar functions. Another mystery seems to be post-infection olfactory dysfunction [219]. Interestingly, the VKDP's Gas 6 and protein S appear to play a regulatory role in the SVZ and in particular olfactory bulb neurogenesis [64].

Common hemotological observations worth noting include elevated d-dimers with mild increase in prothrombin time and mild thrombocytopenia[122] , eosinopenia [126] , lymphopenia commonly with eosinophilia [128] , and leukopenia mostly in younger or asymptomatic patients [235]. Higher neutrophils [60] or neutrphil-to-lymphocyte ratio [130] was found to be predictive of worse outcomes. One recent review found leukocyutosis and leukopenia to correlate with severe disease [90].

The causes for these results are unclear although leukocyte apoptosis is a possible contributor to leukopenia. The fluctuating nature of excess and depletion of some cell types may reflect different disease trajectories of simply that the production and consumption rates vary without correlation to each other. Highly acitvated neutrophils are commonly noted for their damage although explicit reference to NET's and calprotectin was absent until recently [241] and more a request for clnical information on them [152] . One publication did finally find extracellular material including DNA suggestive of NET's [56] . D-dimer may not be too surprising given coagulopathies but interpretation may be open. It has, for example, been considered a biomarker for antihistamine resistant chronic urticaria [12] .

A lot of literature has discussed the affinity of SARS-Cov-2 for ACE2 as a means of cell entry. Lab measurments put the SARS-Cov-2 receptor binding domain affinity for ACE2 in the "low nanomolar" range [115]. Some works have explored increases or decreases of some measures of ACE2 expression. Once translated and trafficked to the plasma membrane it can engage in several processes before meeting one of two fates- internalization or cleavage. Figures such as transcription or translation rate may not be as important as internalization rate which describes how quickly it can turnover and bring in virus. while deployed on the cell surface, ACE2 can hydrolyse AngII to Ang-(1-7) , bind integrin $\beta 1$, associate with neutral amino acid transporter B0AT and be modified with calmodulin to reduce cleavage [34]. These features do not suggest a need for ligand to provoke internalization.

At least one work predicts lower SARS-Cov-2 case counts but higher severity for blacks due to lower ACE2 levels [213] but the dynamics of creation, cleavage, and internalization is complex. Measurable levels of protein may be lower because internalization is faster and the internalization of virus loaded recptors may be the important step. In any case, the current epidemiological data it difficult to sort out due to methodology issues and confounding factors like social policies.

Apparently lacking is any literature linking covid-19 to things like NEDD4. The entry of ACE2 relates to NEDD4 [160] competing with extracellular cleavage to relase a soluble form although as late as 2014 details of the competing fates remained obscure [84] .

2.2. Nutritional issues in covid-19 and related conditions

There is not a lot of literature specifically about SARS-Cov-2 nutritional issues just becasue it has not been around that long but at least one specific motivation for interest in nutrition arises from the recent observation that ileal absorptive cells express ACE2 and appear receptive to infection [238]. One recent report [196] suggested increased arginine and tryptophan metabolism during infection along with "massive suppression of amino acid metabolism." This report also found noteworthy lipid and steroid metabolic changes as well as suppression of platelet factor 4 which has a confusing relationship to protein C [170] [111] .

Nutritional issues for related diseases have been assumed to exist for covid-19 and trendy ideas have been advanced even if historically not effective against these other diseases. For example, at least passing interest was expressed in vitamin C for usage in a clinical trial [29]. Vitamin D status has gotten a lot of attention too, for example [46]. However,these seem to be based on the remaining anti-oxidant hysteria of the last few decades or association studies in the case of vitamin D. Association studies are ambiguous and tend to promote confirmation bias. These can also be interpretted as pointing to other nutrient issues that tend to segregate with vitamin D status. Vitamin D may covary somewhat with vitamin K among others especially when limited by GI issues , for example [192] .

Nutritional immunity, the host's attempt to deprive a pathogen of nutrients, is a well known response to infection. One notable feature common to many infections is the increased activity of IDO to degrade tryptophan. Its overall role remains a topic of research and exceptional status with this virus has not been determined. Tryptophan is observed to be depleted in various conditions such as HIV but supplementation is not always pursued. Instead, IDO inhibition is favored due to the belief that the breakdown products are the bigger problem [153]. It is also known, however, that tryptophan can overcome inhibition of proliferation by IDO products in T-cells and natural killers (see figure 3 for example [58]). Tryptophan depletion per se, regardless of other metabolites is an apoptosis sensitizer [117] and supplementation may prevent apoptosis in the presence of these other metabolites considered deleterious.

Besides tryptophan, phenylalanine metabolism and more directly tyrosine deficiency may be an issue. Dysregulation of tryptophan and phenyalanine metabolism has been studied in HIV [70]. Phenylalanine to tyrosine ratio was observed to increase in HIV-1 patients without treatment suggesting PAH reduction [233]. It has recently been observed that PAH is likely inhibited during several pathological states and these effects are likely to be effects common to many disease states. For example, both have been observed to be depleted during resolution of contact dermatitis [239]. Further interest in tyrosine depleteion may be suggested from age related issues with thyroid hormone [19] [105] ,which has been observed in covid-19 patients [218], or even graying hair as the latter has been related to innate immune activation and viral infection [75]. PKU comorbidities include a large range of conditions that may not entirely relate to excess phenylalanine [207] but rather low tyrosine.

Arginine may be consumed in the generation of NO and exogeneous NO in breathing atmosphere is being explored [143] perhaps more so than arginine status. The interest in nitric oxide against coronavirus dates back at leas to 2005 and SARS [7]. Arginine has been considered in some detail in various infections but question of good or bad remains complex [27] . Interestingly, lysine stimulates HIV growth but this may be largely a virus specific issue [28] as in Feline Herpesvirus it was observed that arginine promotes while lysine retards growth [135]. As lysine and arginine may compete for transporters, there is always a concern when these are a bottleneck.

The coagulopathies possibly relate to NET nucleation and a dysregulated coagulation cascade. Calcium and vitamin K are two important components of this system. One reason for pathological clotting and bleeding may be sudden erratic depletion of fully reduced vitamin K. Some evidence suggests an increase in ischemic strokes for AFIB patients when starting warfarin [106] prior to achieving intended anticoagulation consitent with depletion of protein C and S occuring early on. For other conditions, there is finally controversy over supplementation versus antagonism of viatmin K [24]. There is little doubt that vitamin K contributes to regulated coagulation as well as other functions such as maturation of Gas6, an apoptosis preventor [76], even if the clotting may be the most well known. It has a nuclear receptor like other lipid soluble vitamins [69] and may have wide ranging effects along with its role in gamma carboxylation of calcium binding areas. The vitamin K dependent TAM system - TYRO3, AXL, and MERTK relies on Gas6 and protein S to aid resolution of inflammation [175]. Sometimes VKOR antagonists are cited as anti-fibrotic or having other benefits but some such as 3-acetyl-5-methyltetronic acid, like other small molecules, may have many effects although they are worth consdieration [208] .

One case report series did show protein S deficiency related to Varicella infection,"... six cases of protein S deficiency secondary to varicella. Five cases were complicated by thrombotic and vascular events, namely purpura fulminans and necrotic vasculitis, deep vein thrombosis and stroke. " [158]

Other interesting features of vitamin K exist that may point to relevance in disease and old age. Vitamin K2 was shown to reduce inflammation and ROS production while improving mitochondia performance in the presence of rotenone [222] suggesting at least possible support for some diease related conditions. Lifetime low-phylloquinone diet was associated with cognitive problems in old but not young rats [30].

Possibly the covid-19 skin conditions relate to acute depletion of vitamin K creating both clotting and clot regulation

problems as has been observed with other diseases.

In the diseased state, use of energy and citric acid skeletons is enhanced and depletion of TCA components is a real concern although it may be programmed as part of nutritional immunity. There is some indication that under hypoxic conditions TCA cycle intermdiates are regulated as part of a nutritional immune program [78],

> Citrate, the first intermediate of the Krebs cycle, plays an important role in immunity. For instance, citrate is required for fatty acid biosynthesis, which is involved in mounting an appropriate immune response (Moon et al., 2015). Moreover, citrate can be converted via cis-aconitate to itaconate, which possesses antimicrobial and anti-inflammatory potential (Michelucci et al., 2013). Thus, citrate is thought to form a building block for the production of inflammatory mediators and antimicrobial molecules. However, high levels of citrate may also entertain the proliferation of C. burnetii (Omsland et al., 2008), which is likely to counteract the positive effects of citrate on microbial defense. Citrate is not only important in immunity but also in cancer, as it provides an important source of carbon (Hatzivassiliou et al., 2005; Mycielska et al., 2018). Of note, several cancers are characterized by HIF1a stabilization, which impedes citrate production through oxidative metabolism. Thus, there are remarkable parallels in the regulation of cellular metabolism in immunity and cancer with respect to citrate limitation. However, tumor cells may escape citrate limitation by the use of the reductive carboxylation pathway (Wise et al., 2011);

Citric acid depletion is thought to contribute to disease as it relates to the arginine paradox, [42],

> Therefore, export of intermediates of the cycle is indispensable for anabolic purposes, but also subtracts intermediates that would be recycled to the oxaloacetate, indispensable for condensation with acetate and for maintaining the cycle fully working by forming new citrate. Insufficient oxaloacetate availability into the cycle is followed both by a reduction of energy production and, subsequently, by a reduction of the synthesis of nonessential AA from intermediates of the cycle. This process, however, also triggers the entry of AA into mitochondria to refuel the cycle of oxaloacetate precursors, mostly at the level of succinate or -ketoglutarate. Such phenomena explain the pathophysiological mechanism underlying the sarcopenia/cachexia syndrome occurring in all conditions of peripheral insulin resistance.

Citrate has under lab conditions reduced mobility of calcium and magnesium [162] which may be useful in the presence of leaky membranes.

Calcium status is perhaps not appreciated but just as with citrate in stored blood, regulation with citric acid may be biologically relevant.

3. LIMITATIONS OF CONVENTIONAL ANALYSES

These results differ from others due to being somewhat more speculative but also due to failure of systems analysis based too much on dominant effects . Even though much of the analysis here leads to simply replacing what seems to be missing, it is important to remember thoughts like this [42],

> In this review, conditions influencing the low arginine concentrations found in plasma will be reviewed, *revising the paradigm that simple replenishment of what is lacking will always produce beneficial consequences.* [emphasis added]

Part of the problem is determining what meaningful things are missing after compensatory mechanisms disguise a primary cause. There is plenty of precedent for these issues. For example, one well known confusion occures with the interaction between folate and B-12 in the eldery [100]. In the current situation, older people generally have a lot that is missing but some of that may be adaptive or based on reference values of little diagnostic value.

Several of the ideas here are probably contrary to conventional wisdom simply due to a more complete exploration of cause and effect relationships in light of failures of conventional wisdom to produce useful results or more recent research modifying interpretation of prior observations. In most of the cases described here, the conventional wisdom suggests limiting some nutrient- for example, tryptophan or vitamin K- in a diseased state due to a few prominent (often the first discovered) effects. Vitamin K is known for its role in clot formation but it also contributes to clot regulation on different time scales. So, you could stop clotting by eliminating vitamin K or, better, regulate it with more vitamin K within some range of other parameters. Tryptophan is destroyed by IDO and the metabolites are often thought to be the problem but these may correct with more tryptophan and eventually depletion per se is a problem anyway . The motivation may make sense- indeed nutritional immunity is based on beneficial nutrient loss - but empirically the overall system dynamics may favor the opposite intervention. With age largely predisposing to nutrient loss, anything that effects old people should elicit a concern about nutritional dependencies.

Once a molecule is catagorized as a clotting factor or some other trendy thing like antioxidant it tends to become good or evil and new obervations may be rationalized in terms of these first known effects. Or, for lack of a better catch phrase, " chemical X is a Z so it can't do Y" [139]. In the case of vitamin K, clinical success antagonising it makes it difficult to accept evidence that more may be even better under many conditions.

There is also a lot of interest in easy to analyze solutions as ,by definition, they are easy to understand - one drug, one target for example. Small molecules are often problematic due to off target effects and more selective antibodies are desirable due to more specific location of action. However, for nutritional interventions the target is often a well regulated metabolic network and trying to find general rules like " more is better" is difficult. Monotonic dose-response curves robust against other factors may not be very common. Further, a single point of failure may require multiple nutrients for remediation before much benefit is observed. It may not be possible to even vary "one thing at a time" to get an unambiguous error signal let alone a cure. Before concluding much based on one effect, it is probably better to actively hunt for compensating mechanisms that create a time or metabolite differential or ratio or something similar.

Food association studies may be another source of difference. These tend to create confirmation bias around something trendy like vitamin C. Much of this analysis was explored after rejecting assumptions about anti-oxidants as the dominant nutrients of value. Earlier a case was made against tocopherols [140] that better agrees with known clinical data. And as is often the case, inconsitent association studies may point to more compilcated causal relationships or none at all if the independent variable happens to have a misleading correlation. Another interesting observation is the apparent benefit of citrate against cancer [173] which could explain many food relaed help benefits often ascribed to vitamin C. . Anti-oxidants as a class have been over rated and ROS signalling is now well known but the myths persist.

Correlations may also occur in shared pathways and a trendy vitamin's associations may mask a more important one with shared statistics. One trendy vitamin , vitamin D for example, could be confused with vitamin K in some observational studies and even intervention where it provides a partial solution. Vitamin D stimulates secrtion of vitamin K dependent proteins and is even suggested to work by synergry with vitamin K [89] but presumably does not replace vitamin K for gamma carboxylation.

4. OVERVIEW OF MY "OLD AGE AS STARVATION" WORK

In my theory of aging notes [141], I try to motivate the case for aging being largely the result of GI problems and nutritional issues but not the ones commonly considered - or in essence starvation. The relationship to usual types of starvation is not obvious because the dynamics of age related nutrient deprivation are not typical of classical forms of starvation as compensatory systems can do a good job moving the problem around. Initial results attempting to optimize dog diets have guided the selection of important nutrients.

There is recognition that poor nutrition plays some role in aging but most of the literature assumes it is an effect of conditions such as loss of taste or a stroke [121] rather than a cause. Others concentrate on a trendy, incomplete set of nutrients. Possibly the age related damage is part of a positive feedback loop and malnutrition creates more damage that makes nutrient uptake even more difficult. In some cases, correction of the right nutrients in huge non-competing doses may allow for passive diffusion in place of normal damaged mechanisms. Considering low acid and enzymes as part of a positive feedback loop that continues to decrease the supply of things they absorb, it is worthwhile to consider the known nutrients likely to be effected and determine that supplementation is complete enough to fix identifiable problems. Much literature seems to state as fact that some subset of nutrient is responsible for some effects but the evidence is not clear.

One feature of old age in this scenario is amino acid starvation with muscle wasting being largely due to attempts to scavenge amino acids. The loss is likely not uniform and chronic stimulation of IDO may slowly deplete tryptophan preferntially as seen in diseased state. In essence the body is in a state of chronic low level disease combined with a specific absorption problem. One interesting work found mutation in an amino acid transporter , SLC7A8, that effects age related hearing loss [72]. This may suggest an imbalance of amino acids could occur in old age although replacement of any particular one may not be the solution.

Generally, lower proton(acid), chloride and enzyme levels can be expected in old age and broad areas of concerns are metals, amino acids, things attached to proteins, and fat soluble vitamins. Depending on the pH preferences of the enzymes, acid alone may be a big factor and oral enzyme replacement of limited value. One common reason in old age may be "atrophic gastritis" which would not be obviously related to an acute disease. Adding acid to meals does apparently help folate and B-12 absorption [177]. This source then goes on to consider absorption of vitamin D decrease with age as only an effect and not so much a cause. It also singles out iron with no comments on other cations. "Things attached to proteins" could include biotin or the better known issue with B-12 Literature on amino acid supplements for humans has had mixed results but this is probably atrributable to inability to balance the amino

acid pool, lack of availability of hydrophobics like tryptophan and valine, and lack of associated components like citric acid for metabolic flexibility.

In cases where its impact on nutrition is considered, analysis may just be confined to trendy vitamins. One recent article suggested vitamin C was needed for serotonin and norepinephrine production as well as collagen [32] but neglected stoichiometic amino acid requirements and copper for crosslinking. Correcting the suspects discussed here did seem to help several older dogs although several other additions such as B vitamins were included too (unpublished observations). In the case of covid-19 , only those that seemed to help the dogs and appear relevant to the SARS-Cov-2 are included.

Low stomach acid and enzymes would be expected to deplete amino acids and things attached to proteins as well as cations with lower solubility. In some documented cases, significant GI disruptions including bacterial overgrowth can impair all fat soluble vitamin levels but leave vitamin K as the most important [163]. Also note that nutrient absorption is not the same a fat absorption. Initial results feeding these nutrients to old dogs have been encouraging [141]. Recent work suggesting utility of vitamin K for age related conditions[199] appears to be the less common view. The symptoms of old age empirically suggest vitamin K deficiency is likely a big contributor but there seems to be a general concern about giving vitamin K to old animals or people. In particular, there has been no indication of severe problems with vitamin K in older dogs. Recently up to 10mg/day K1 and 15mg / day K2 have produced no obvious problems and may be contributing to recovery in 5-30kg dogs. With a background of amino acids, copper, citric acid but little zinc even in the presence of heartworm vitamin K appeared safe in one dog although a therapeutic role could not be determined and coughing symptoms did worsen coincident with the addition of aromatic amino acids [138]. While some age related conditions like osteoporsis may appear to be issues with cations like calcium, those may in fact be more related to amino acids, vitamin K, citric acid, and nutrient signalling. That is, to form the proper calcium minerals, collagen scaffold needs to exist using the required amino acids and conditions need to encourage appatite nucleation and growth. Added calcium may help density but may not create normal stength bone and rather precipitate calcium all over.

Tryptophan depletion seems to correlate with aging [210] [211] although it is not clear if tryptophan depletion per se is an issue and generally there is a focus on disabling TDO and IDO. Metabolic changes may occur with many nutrients and sorting out cause and effect may be difficult. In particular, dog breed longeivity appears to correlate with tryptophan metabolism [87]. In extreme depletion, protein synthesis will suffer and uncharged tRNA can accumulate [232] . Low fidelity translation can occur due to lack of one amino acid or the mischarging due to amino acid analogues competing with the limited supply of accurate ones. This can become toxic in many ways but one possible problem is replacement of a tryptophan with something smaller in a transmembrane region one result of this is ion leak which may cause many age related diseases. Amino acid supplements for old people demonstrate some reports of success [157] but results do not appear to be consistent as the varying details may prevent consistent success [224] [93] . This may be due partially to gettting a complete mix of components that solve existing problems without creating more of them. This work is not based on any of these but rather an analysis of what is likely to be missing. Originally it would have been easy to dismiss tyrosine as non-essential except for some quick literature search and feeding experience with dogs sugests it as an important contributor to stressful conditions like aging or disease.

Copper has gained attention lately as being important to cardiovascular disease , specifically ischaemic heart disease [41] which may be a concern with exaggerated coagulopathies It has been well known to facilitate killing by macrophages [55] . While the theory suggests many cations like amino acids will be lacking, copper is likely the most important to address. Pharmacological supplements of zinc and copper fed to newly weaned piglets reversibly modified microbiota and improved intestinal health [156] which may be important in older or diseased people.

Many of these issues would benefit from acid consumed with meals for which citric acid may be a good choice. The citrate has other benefits that may be important for calcium control and metabolic flexibility.

5. DISCUSSION - APPROACHING SARS-COV-2 AS A NUTRITIONAL DISEASE

If the age dependence of SARS-Cov-2 severity can be explained in terms of nutrients involved in my aging theory, then it should be possible to reduce both disease severity and typical age related diseases by modifying the status of these nutrients. The obesrvation of a SARS-Cov-2 related syndrome in children with prolonged or second disease course may be rationalized as nutrient depletion similar to that theorized to occur in old people. Young children need protein synthesis to grow more than middle aged although they both presumably have well functioning GI tracts. If the disease can damage GI tract and deplete nutrients eventually similar nutritional situations may arise.

The above considerations lead to suggestions that depart from most published notions about related diseases and aging. The contoversial issues largely involve benefits from tryptophan and vitamin K while adding possible benfits from tyrosine, copper and citric acid while agreeing with some ideas related to ambiguity about argnine or nitric

oxide. There is no obvious involvement of antioxidants or other trendy nutrients for most people eating a Western diet although as noted , especially in old age, broard systems could be damaged requiring a range of nutrients until function is restored. The ones mentioned here would likely be the most important and able to show benefit on their own in many cases.

While a specific protocol is not yet defined, adding these nutrients incrememntally and observing intial results may be useful for formulating a specific therapy. Any approach should be designed initially to create data not hypothesis test. Hopefully the details are not that critical however some patients may have idiosyncratic issues such as protein S deficiencies and evaluation of the more controversial items may benefit from better monitoring.

5.1. ACE2 and age related conditions

ACE2 received a lot of attention related to SARS-Cov-2 and is known to be part of the blood pressure issues common in older people. However, apparently lacking is any literature linking covid-19 to things like NEDD4. The entry of ACE2 relates to NEDD4 [160] competing with extracellular cleavage to relase a soluble form although as late as 2014 details of the competing fates remained obscure [84] . Reiterating the ealier point, NEDD4 is an attractive speculative internalization rate controller as it senses a common attribute of many predisposing conditions. The old age theory suggests ion leakge due to defective membrane spanning proteins among other reasons and this would presumably increase NEDD4 activity.

Expression of ACE2 was recently shown to be interferon stimulated in humans [238] leading to the suggestion that infection should increase the net amount of ACE2 on the surface. NEDD4 is downregulated by ISG15 in response to inteferon stimulated by many virus infections such as " influenza, herpes, Sindbis, and HIV " and apparently can reduce Ebola VLP release [136]. Both of these may allow for more surface expression and cleavage. NEDD4 has many recognized functions [91] but as a cytosolic sodium sensor, culling sodium channels to maintain intracellular sodium levels, it could be expected to be more active in cases of sodium leak or intracellular excess. NEDD4 also responds to calcium [215] which may be a bigger issue than sodium as maintaining submicromolar concentrations could be more difficult. NEDD4 has been shown to use, " 1)ion channels and transporters, 2)membrane receptors, 3)tumor suppressors, and 4) endocytic rgulation proteins" as substrates [215]. Anything which causes upregulation may result in culling of many things suggesting intracelllar starvation would be possible under the same conditions that enhance viral entry.

Interestingly, ADAM17, the protease creating the soluble cleavage product, appears to be stimulated by thrombin [132] which may reduce infectvity suggesting a benefit for the virus coagulation inhibition.

Artificially introduced cmRNA for ACE2 was found to benefit from codon optimization which at least partially works by switching to a more abundant synonym [187]. This does not address amino acid starvation explicitly but rather the abundance of charged tRNA which directly is impacted by amino acid starvation.

5.2. Citric acid

Citric acid is expected to have benefits by controlling calcium and replenishing TCA skeletons in the presence of increased metabolic loads. Some evidence exists for immunmodulation and related effects [5]. It may also be metabolized to bicarbonate . The transfustion literature is full of interesting observations (for example [88]) It may also be instructive to look at earlier observations for its "obscure " role in pH regulation noted since at least 1933 [114] [188] .

However, it seems to be ignored in food association studies that look for vitamin C or flavonoid effects. For example, in one study most of the beneficial foods [96] have high amounts of citric acid or other organic acids . This is despite it being the central skeleton in the citric acid cycle which can be depleted during heavy metabolic demands. It may turn out that many benefits attributed to vitamin C are really due to citric acid and prove to be another food association misinterpretation. There is some indication that 3grams/day can reduce fatigue [203]

Calcium control can influence both signalling and precipitation. Accumulated precipitates may be common in old age and virally induced whereas inappropriate signalling may occur due to leaky membranes or in various calcium dependent processes such as coagulation. As a metal chelator, it may help distribute calcium and other metals. Dietary orgnic acids including citric acid have been explored for thrombus management with some indication of effect [99].

The TCA turnover may increase in any "stressful" situation such as SARS-Cov-2 infection or common conditions of old age. Fever in children has been associated with increased heat production of 11.3% per C and increased nitrogen excretion [18]. Protein-calorie malnutrition is common in the critically ill at least in part due to increased resting energy expenditure [189]. It has been generally known that infection increases demands for amino acids [165] as part

of a larger metabolic turnover. These may all seem unrelated but the metabolism of unbalanced amino acids often proceeds through the TCA with significant effect on energy flow [17].

While fever is a well known common result of SARS-Cov-2 infection, it is notable that there is no indication yet of any calcifications related to SARS-Cov-2 [97] [77] although they may take time to grow to discernable size. Intracranial calcifications detectable with CT can be caused by several viruses [178] and appear to be best known for fetal infections. Mineralized avian influenza virus has been recently observed and the minerals thought to contribute to stability [236]. Ion permeability increases including for calcium are well known for HIV to encrouage its survival and translation of the viral mRNA [36] but literature on coronavirus was not found.

Citrate may be best known in blood preservation and kidney stone literature but similar priniciples operate in i*in vivo* blood but with different scales.

5.3. Amino acids

Amino acid nutrition may be relevant due to metabolic changes, GI digestive efficiency,increased protein synthesis, or changes in transporter distribution. In old age, the GI problems are thought to be primary but in the disease state the others may be most important. The common themes in disease and aging point mostly to tryptophan, tyrosine, and arginine with maybe some importance for others like valine. As they may compete and shift metabolism, benefits from essential or broad supplementation may not exceed those of a selective approach which can balance the pools in light of excess metabolism or altered transport in the disease state. At least with IBD, broad spectrum supplementation at normal levels is recognized as a possible problem compared to targeted high-dose supplements [65]. One notable issue with extreme imbalance is the amino acid pool available for charging tRNA and the effects on protein synthesis rate and fidelity as well as signalling by uncharged tRNA and charging synthases. The latter is an emerging field with roles being elucidated in nutrient sensing and cellular adaptions to starvation [79] [25] [166] Amino acid considerations in the disease state have been explored before, in one case leading to a formulation called CATHON but also pointing to depletion of TCA skeletons [42]. It is likely to be easier to make non-essential amino acids if the TCA is fed with citric acid. In the aged state chronic low level infections may be a problem but the primary GI issues may favor a more comprehensive amino acid mixture while still favoring these beyond normal abundances. Lists of well known functions exist, such as [124], and supplement modificions could be designed in response to outcome. After taking care of these, there may be more issues that become apparent as, besides the B0AT transporter associated with ACE2, amino acid transporters come up in more and more contexts often related to mTOR or immunity. For example, SLC15A4 [108] just came up in the context of endolysosomal transport related to SLE [82] .

Thinking outloud
mischarging with amino acid analogs would depend on the existence of such analogs which could be of microbial origin or maybe host. These may not compete until the parent amino acid is in short supply.

After making this list of amino acids, it became apparent that the amino acids most prominently highlighted all are in pathways using tetrahydrobiopterin (BH4) [155] which, along with neopterin, reacts to disease[146] [47]. One work from 1961 that only knew of PAH as a possible pteridine indicated the conversion to tyrosine was slowed with methotrexate [67] and it is interesting to speculate on nutritional immunity playing a role via folate or look for follow up work. One recent survey of cytokine storm markers in SARS-Cov-2 patients lists neopterin as "not assessed" [83]. Interestingly, neopterin levels were found to inversely correlate with survival in elderly hip fracture patients [116] suggestive of related processes occuring in this group. Phenyalanine stimulates the activity of tetrahydrobiopterin [124] and PAH downregulation appears to be common in the diseased state. If Phe stimulation does not over come other sources of downregulation. this leads to concerns about the essentiality of tyrosine but also Phe toxicity and reasons to be suspicious of supplementation.

Tryptophan is the well known target of IDO and TDO. Earlier works on metabolites demonstrated some activity of the metabolites suggesting IDO inhibitors would be more important than tryptophan supplements but at least one work's data showed tryptophan prevented the bad things. This protection may be quite diverse. For example, yeast exposed to SDS are more resistant with tryptophan [186] and as described below there may be detergent like effects from membrane spanning proteins mistranslated at tryptophan sites.

Being rare to begin and a precursor to consumables , it is easy to speculate that it gets depleted quickly and could get to the point of making high fidelity protein translation diffiult leading to non-specific problems and futile cycling of defective proteins. Specifically, with a role in sealing membrane bound proteins, it is a good suspect for possible ion leaks at low fidelity products that make it to the plasma membrane. This would likely be mostly sodium and calcium inbound. Sodium would likely lead to swelling commonly observed in infection and calcium signalling would be chronically stimulated and eventually could lead to precipitation [137] . Further speculation suggests citric acid

could minimize calcium leakage and help maintain sub micromolar cytosolic levels. This leakage is likely a natural component of many old age diseases including hgh blood pressure.

Any amino acid pool imbalance may stall ribosomes and produce defective proteins for both host and virus. Trytptophan and tyrosine appear to be prefered at membrane interfaces likely due to large rigid planar structure [229].

Certainly with GI issues as may occur with old age and probably with SARS-Cov-2 , improving solubility may help. Wetting of tryptophan powder for example appears to improve with calcium pantothenate powder although reactions and degradation of both may need to be explored. In general, it is good to remember these things are matierals not just nutrients [139].

Interestingly, tryptophan to niacin conversion appears to be decreased in women due to hormonal control [197]. Women do tend to live longer and have less severe covid-19 although statistics on various groups of women and men with varied hormone status would be needed to demonstrate an important correlation.

Tyrosine I originally dismissed and there may be more suprises but a recent in silico drug discovery effor for SARS-Cov-2 turned up targets including several carboxylases and homogentisate 1,2 dioxygenase [31] which is part of the tyrosine degradation pathway. It did appear to be beneficial in old dogs and maybe my grey hair(unpublished observation) . Observations of increased Phe/Tyr in HIV patients cited earlier suggest it may be decreased. Depression related to interferon-alpha may be due to tyrosine decrease [54]. Other work suggests biopterin remains intact during ifn-alpha treatment [68]. The need for MAOI's to make even high doses of tryptophan effective against depression [151] further suggests a role for tyrosine in some cases(for an interesting discussion of misconceptions see [85]) .

Tyrosine is not normally considered essential, although see the CATHON paper [42]. , and often nutrition assays quote tyrosine plus phenylalanine [62] as if they are interconvertable . The prior reference also points out that unsuccessful supplements for kidney patients lack tyrosine, even though reduced conversion is observed [109] , and anecdotal evidence supports addition of tyrosine to achieve positive nitrogen balance.

If tyrosine is a virulence limiting molecule, then people with increased demands due to highly pigmented hair or skin may be at additional risk or have metabolic flow already somewhat adjusted.

For SARS-Cov-2 intervention relationship to phenylalanine may need consideration. Phenylalanine or tyrosine dietary restriction was sufficient to indpuce lymphocytopenia in mice and modulate natural killer activity [147]. One reason for the observed low cell counts with SARS-Cov-2 could reasonable nutrient depletion. However, phenylalanine may spontaneously be hydroxylated to an m- or o- tyrosine isomer and the latter two may produce contominant resitance among tumors due to tRNA mischarging [176]. Interestingly, phenylalanine and histidine appear to minimize this resistance although direct relevance to SARS-Cov-2 is unclear. Tyrosine mistranslation as phenylalanine or histidine is often observed in CHO antibody production and it can be corrected with supplemental tyrosine [52] although this does not prove it is ever significant in mammals it does establish plausbility. In any case, selective supplementation avoiding phenylalanine and histidine may be worth exploration.

Thinking outloud
An interesting example of wide ranging effects of amino acid depletion is the case of poisoning by the common food contaminant Ochratoxin A. A lethal dose for mice can be overcome with a similar weight of phenylalanine [37]. The mischarging of Phe-tRNA creates kidney and liver problems that may be difficult to identify in the case of lower levels of multiple problems.

There are various claims about arginine anti-aging effects [59] Arginine is somewhat controversial as it has shown bad results in some clinical trials [223] and is not considered essential, maybe semi-esential , for healthy humans but its interactions with copper and lysine may need to be considered.

At least one study with agings rats suggesed that age related declines in NO were not likely to be due to arginine synthesis declines [149] although age related declines in absorption may still be an issue as endogenous production may not be sufficient with increased demands. A similar ambiguity may exist with tyrosine which can be produced but also supplied through a normally functioning GI tract.

One interesting work demonstrated teratogencity due to low copper and nitric oxide [228] demonstrating its signalling role and interaction with copper. This is in addition to NO and copper as they relate to vasodilation [66].

Another study found good reason to look for food association with improved health in the elderly but found none [164]. Food association studies can be confounded and in the case of the elderly multiple nutrient deficiencies may need to be corrected to see any clinical improvements.

Nitric oxide was identified previously as suppressing an earlier SARS in vitro through unexpected mechanisms of decreased RNA production and spike protein post translational modification reduction [8]. Clinical trials involving NO inhalation are being designed for these reasons [119].

Arginine could be depleted due to beneficial NO production. However, there have been some concerns raise and with the dogs a few suspicious results even with lysine supplementation. One trial with many people over 60 and ST-segment elevation MI demonstrated excess deaths in the arginine arm leading to trial stop [190]. Arginine has been observed to improve cellular immune response [92].

Valine is possible good as some publications have found effects on virus behavior . There is some indication it can imprvoe DC maturation in normal and HCV patients [101] and supplemented with interferon appeared to benefit and HCV infection [103] . Interestingly, turnip yellow mosaic virus apparently contains a sequence that can esterfy valine or tRNA like behavor [231] although general effects of virus on amino acid or tRNA's remain to be explored.

5.4. Trace nutients normally associated with protien

In the presence of a protein digestion issue it is likely trace nutrients associated with proteins will be deficient too. Biotin for example and all SMVT substrates in rotation. However, there is no indication the disease state increases consumption of these significantly.

5.5. Metals, atomic cations

The aging theory suggests many trace metals will be in short supply especially with popular emphasis on calcium and iron crowding the others out. Among the possible victims are copper, zinc, magnesium, and manganese. The symptoms of olad age and SARS-Cov-2 disease suggest copper is a dominant problem in both.

Thinking outloud
In some informal feeding experience with old dogs, the copper and zinc seemed most important although magnesium and manganese were included. Copper without zinc eventually created some feeding hesitancy which resolved with zinc. Incidents of diarhea seemed to decrease but otherwise not sure Other work suggests copper would probably be the most relevant forgotten nutrient related to SARS-Cov-2 .

Early results with mice demonstrated an indication that copper deficiency could prolong clotting times and, at least in female mice, promote thrombotic lesions [133]. By 2000, it was a recognized problem with heart and vascular disease from a Western diet [107]. Some of the features of old age would likely manifest slowly such as the lack of crosslinking. In the acute disease setting, different effect may matter.

One issue with SARS-Cov-2 treatment is QTc related to hydroxychloroquine. While not discussed much in modern literature, earlier arthritis work uses this along with ACE inhibitor captopril as examples of possibly effective treatments due to copper manipulation [22] .As it is also used to treat prophyria cutanea tarda, an iron related disease [200], and has retinal side effects similar to deferoxamine [40]. Chlroquine is often described as a zinc ionophore with little relationship to iron or copper [225].

One study found measurements of QT interval such as QTc tended to get worse with low copper rather than low zinc [94]. While copper can shift voltage dependence of potassium channels, a concern for QTc elongation, deficiency was seen in 1999 to have an effect on calcium tolerance that is not correctable with calcium channel blockers [171]. Literature on cardiac involvement seems to be lacking but a recent result summarizing metal ion modulation of ion channels demonstrated an important interaction between copper and a calcium channel in the retina [134] which is likely to represent a common interaction.

One othe work [92] suggests including copper in a diet directed at SARS-Cov-2 .

Like with the other nutrients, the sequesteration of copper could leave the host cells with an effective deficiency. Clotting and fibrinolysis both appear to be modulated by copper but in non-obvious ways presumably to allow robust responses in most situations. Some of the known regulatory pathways suggest it would be impossible to say in isolation if more or less copper would be better or worse but generally the disease and old age symptoms make more sense as insufficient copper. One interesting case is the effect of copper on PAI-1 which can either increase or decrease stability depending on the presence of vitronectin [26].

Copper is generally thought to be a target for nutritional immunity along with iron and zinc but the extent of this may not be well determined [20] . Calprotectin, a calcium modulated zinc binder composed of S100 [221] alarmin members, was just found in 2018 to bind copper with subpicomolar affinity [21] (also nickel [131]). COMMD1/Murr1 is the means of biliary copper loss and also involved in ion homesostasis elsewhere and a known HIV-1 restriction factor [205] . Interestingly, it also works with NEDD4-2 to remove epithelial sodium channels [104] in an activity which

presumably increases in the presence of sodium leak which this theory predicts increases due to misincorporation at tryptophan codons. For a recent review of ion channel regulation see for example [161] .

Interestingly, copper apparently can inhibit activated protein C's anticoagulant activity but not with human serum albumin present [16] .

Copper is generally added to the phagosome under infection conditions [73] . Indeed, copper has been observed to reduce susceptibility to coxsackievirus although the mechanisms remain unknown [86]. In the presence of possible ADE, any additional neutralization may help if the virus can be exposed to copper prior to emerging.

For some reason, zinc has attracted a lot of popular attention as an antiviral and specifically is thought to work well with hydroxychlorquine. The latter likely is a significant broad spectrum chelator as well as an ERGIC inhibitor. Even in this combination, copper may at minimum reduce side effects.

Some literature suggests that copper is more likely to cause inflammation or other pathological immune responses [184] ZZ .

Recent literature and experience have pointed to a larger role for copper that would likely be especially true with zinc supplements. Copper has recently been appreciated for its role in killing or modulating the virulence of bacteria. Many seem surprised it is an essential nutrient even if they know about zinc.

In general the metals compete with each other. In terms of reaction to the virus, while many people may benefit from most metals, nutritional immunity may be favored with excess copper and zinc depletion.

The coronavirus envelope protein, a viroporin, was compared to the influenza M2 [185] which can be inhibited with copper. It is not clear if SARS-Cov-2 has any proteins significantly effected by excess copper although that may compete with zinc.

While not strictly a nutrient, another metal , bismuth could also be suggested for inhibtion of viral helicase.

Bismuth is also considered beneficial here for virus specific reasons althought its reputed broader antibacterial roles may benefit the GI tract.

5.6. Fat solubles : A,D,E,K

The pattern of cutaneous symptoms and general blood parameters (elevated d-dimers, mild increase in prothrombin time, mild thrombocytopenia[122]) is not inconsistent with depletion of proteins S and C and coagulant factors as would be expected from a fast loss of reduced vitamin K. The covid-19 skin features may relate to acute depletion of vitamin K creating both clotting and clot regulation problems as has been observed with other diseases. Elucidated roles for protein C, protein S, and Gas6 [76] all suggest a useful role against the pathological immune response similar to that observed in covid-19 patients. Notably Gas6 tends to suppress apoptosis which may be a cotributor to disease progression. Very recently, reduced functional vitamin K status infered from increased uncarboxylated matrix Gla protein was correlated with elastin degradation and COPD ([168]) was correlated with worse outcome in covid-19 [43]. Direct measurements are lacking at this point but vitamin K deficiency is often ignored and at least one report described misdiagnossis as DIC [9]. One case report abstract noted that infection associated skin lesions can resemble warfarin induced leading to detection of protein C and S deficiencies in their patient [44] but it does not sound common to suspect this. Another case report of infant suggests differential diagnosis of purpuric skin lesions can include suspects including Kawasaki disease and association with various infections [11]. It is also interesting to note that SARS-CoV nsp10 interacts with NADH4L [125] which speculatively may allow it to mutate to interact with VKORC or other proteins with vaguely similar functions.

Protein S and C defects or deficiencies are known or suspected to play many roles in coagulopathies [127] although involvement of vitamin K is not always addressed. Decreased protein S was observed in children with varicella infection [113]. Increased D-dimer and reduced protein S can occur during pregnancy [110] and in children with HIV [169]. With liver involvement, many result are possible as coagulant and anticoaulant proteins suffer as well as clearance in the case of d-dimers [159]. Note also possibility of hypocitremia under disease conditions leading to lack of calcium control in the clotting system.

Loss of reduced vitamin K forms would benefit the virus in several ways. While host factors would be considered, there is some indication of a virus specific reasions. Vitamin K3 exhibited an IC-50 of about $8\mu M$ against SARS-Cov-2 Mpro [80] encoded from nsp5 [13]. This does appear to motivate a survival benefit from inhibiting availability of vitamin K and perhaps the epoxide form is not suitable for viral inhibition. This may be accomplished if nsp10 has mutated to inhibit VKOR locally. Menadione may not be a good dietary choice but phylloquinone can be converted to it [195]. It is probably woth noting that menadione has also been observed to inhibit IDO to a recognizable degree[112] and is also a carbonic anhydrase inhibitor [33]. Loss of vitamin K may then explain reduced blood CO_2 if carbonic anhdrases are limited by mednadione.

Host factors could include anything that modulates protein synthesis or immune defenses such as clotting. Precedents with other viruses are known. Receptors Tyro3, Axl, and Mertk with immuunomodulating properties and

interaction with viral pathogens have vitamin K dependent ligands [198].

Among host factors, clotting is the most obvious but there are many other vitamin K modulated systems. One overlooked observation is the role for vitamin K1 in embryogenesis. Observed in chicks in 1997 [183] it appears to be programmed suggesting physiological mechanism for reduced vitamin K activity. This may be due to a change in programming to that may facilitiate virus replication. Note that this alone may not be a dominant feature as neonates do not appear at high risk for severe disease although there may be few cases of infection.

A 2019 review on aging issues involving vitamin K list several modes of action including on androgen receptors with a pro-cancer effect [14]. The sex distribution in SARS-Cov-2 patients is skewed towards males and this may be a negative factor. i

A few years ago it was noted that warfarin appeared to decrease survival in idiopathic pulmonary fibrosis patients not needing anticoagulation [220] highlighting the possiblity of vitamin K contribution to healing problems associated with SARS-Cov-2 infection.

Fully rediced vitamin K is needed to gamma carboxylate and form calcium binding sites. There are two obvious ways to create an effective depletion of vitamin K dependent proteins. One is to make the vitamin K unavailable either by sequestering, or eliminating. Another is to prevent it from being reduced by VKORC. Vitamin E apparently effects supply as α tocopherol selectively depletes extra-hepatic phylloquinone (but not menaquinone) [74]. Interestingly, quinone impurities in vitamin E can inhibit vitamin K carboxylation in very small quantitites [45]. The above source also points out that reductions in ischemic stroke by vitamin E seem to be "balanced" by hemoraghic stroke suggesting something like copper or citrate may be a more accurate approach for clotting problems.

If cycling is being inhibited, there is some suggestion vitamin C could help [95] but there is only inconsistent indication it interferes with warfarin some reports suggesting no clinical relevance [53] while the prescribing information does list high-dose vitamin C as a interaction concern [2] as would be expected if it had clinical benefit on VKOR cycling. At least one case report exists in which a patient on warfarin and vitamin C experienced various symptoms due to clotting which resolved with vitamin C withdrawl [181]. Possibly the vitamin C effects the clotting part more than the other functions as both apparently can be selectively targeted somewhat.

It is worth discussing the less suspicious fat soluble vitamins because attention to them may be due to confusion with vitamin K as some evidence does not discriminate well. Currently, vitamin D gets most of the popular press attention due to relationship to calcium and prior to that vitamin E because it could be called an "anti-oxidant." However, vitamin K is the most important based on this analysis .There is some indication that vitamins D and K may associate somewhat whereas E and A can antagonize K. In any case, the interactions may confuse discovery of the primary causes of disease and current interest in D may be more appropriately directed at K. For one recent review on vitamin K, see [194].

Vitamin D is known to effect NEDD4 in two ways. In an indirect way, the increase of serum calcium could increase cytosolic calcium due to leaks and activation of NEDD4. More directly however, the active form of vitamin D (minority in the blood) $1,25\,(OH)_2\,D_3$, at least at high doses

Thinking outloud
(blot looks like control smaller than low dose)

was able to reduce NEDD4 expression at least in VSMC's [118] . It is worth noting in passing that [118] also described a good mechanism for general infection stimulated mineralization which I think leads to other age relaed diseases of putative infectious origin including Alzheimer's.

As a known inhibitor or vitamin K, vitamin E and certainly the more confusing mixed tocopherols should be avoided. There is at least passing concern about them in this context [71] aside from deleterious clinical trial results. I outlined a larger issue with overuse of antioxidants and in particular tocopherols earlier [142].

Vitamin A has not been considered.

5.7. Integration

If SARS-Cov-2 provokes similar nutritional problems as related viruses and if my aging theories have merit, the combination of amino acids, copper, citric acid, and vitamin K may be helpful in both conditions. Some of these work together but most could provide some testable benefits individually. There may be concern about vitamin K producing pathological clotting among those with protein S or C problems, elevated calcium, or those withouth sufficient copper or citric acid. Any vitamin's benefit can be limited by others and idiosyncratic deficiencies may need additional consideration. More widespread deficiencies may be more likely in the chronic setting that includes old age or a prolonged infection but not as much for an acute disease.

[2] https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/009218s108lbl.pdf

The most important amino acids appear to be tryptophan, tyrosine and maybe arginine or valine (not discussed in detail). It is not clear if other amino acids would help although some such as phenylalanine and histidine may be deleterious. One realistic concern is not just an asbolute deficiency but not enough of one nutrient to allow others to be used properly. Balancing the amino acid pool for fast high fidelity translation and appropriate signalling from the tRNA assembly pathway is one concern. Adaptations can occur too as the interferon gamma of the disease state may divert more tryptophan to protein synthesis, at least in cancer cells, [6] but there is a lot less of it. These amino acids were highlighted due to them being consumed preferentially by disease processes.

Among the metals, copper is likely the most important to consider and zinc may be important but overempasized to the detriment of copper repletion. It often appears to be the metal that limits use of other nutrients at least under lab conditions. For example, issues with fructose and NAFLD [202] which also may be relevant as obseity, or more inclusively fat to muscle ratio, appears to be a covid-19 risk factor [182]. I tend to rotate metals for the dogs, working in magnesium and manganese. For a while, the vitamin K was given with a zinc deficient diet which may have had some impact. Bismuth may have some utility against SARS-Cov-2 but as part of a virus directed therapy [227] and not an age related nutrient issue. Overall metal balance may be effected by dietary acid or sulfur sources. Taurine or garlic was commonly included im the dog diets with some early indication of a benefit from garlic.

Vitamin K and citric acid may also be useful despite the concern about coagulopathy and the almost placebo-like attitude towards citric acid. The disease severity correlation with old age and vitamin K status suggests that vitamin K levels may be enough to overcome any VKOR inhibition if it exists at all. The citric acid should provide metabolic flexibility in the presence of imbalanced amino acid levels and better control over calcium and metals.

A complete formulation must recognize inteactions with each other and patient as well as the materials properies and chemistries of these components and their environments. Lecithin and pantothenate may act as emulsifiers for the more hydrophobic components although reactions and degradation need to be considered. Both valine and tryptophan appear to wet and suspend better with pantothenate while the lecithin does not appear as effective(unpublished observations). It is not clear if any of the emulsifiers aid absorption although these details may explain inconsistent or confusing results in past literature. It is never really possible to test "one thing" at a time as the drug being tested is effected by every other detail.

The limited experience with self and dogs provided some specific results but have not yet been organized. Diets were more complex that the concepts presented here but the isolated nutrients may capture much of the virus specific requirements. The vitamin K used was typically K2 as mixture of MK-4 and MK-7 in 15mg capsules[4]. Addition of bulk K1 powder in dextrin[1] appeared to have some additional benfits but this change was not made in isolation. Copper was usually obtained as citrate [3] or glycinate[2]. Any food quality citric acid powder is likely equivalent and various diet or energy drinks may contain substantial amounts.

Therapeutic or counterproductive effects may be quick to assess. If the cutaneous issues with SARS-Cov-2 are due to coagulopathies, additional vitamin K or even copper or citric acid may create visible changes within days although disease trajectory likely varies on similar time scales requiring better control and statistical analysis. Citric acid's impact on metabolism could occur within hours, indeed impact on calcium could be within minutes, and any fatigue reduction could be on similar time scales. All clinical signs would likely be subtle. If it helps dissolve clots, clean up metals, and replenish TCA skeletons effects on various times scales may occur.

The contributions of amino acids may be more difficult to assess. Tryptophan depletion in the case of aging will likely create leaky membranes leading to sodium and calcium influx activating NEDD4 and promoting low level swelling. In the acute case, recently translated proteins including antibodies will suffer and signalling related to uncharged tRNA will occur . Apoptosis may be a problem especially in effector cells. Response to repletion may be notable in days. Tyrosine may have some similar issues if PAH shuts down. Both are precursors to neurotransmitters and thought to produce mood disorders when deficient [123] although controversy exists [167] . As an altnerative to tryptophan, possibly niacin supplementation would reduce the loss of tryptophan (discussed in terms of NAD etc in [81], observed in HIV paitents [154]) as it can be a significant sink (and also note the ability of another essential amino acid, leucine, to make this worse) [15]. Pellagra response to treatment typically occurs within days or weeks and presumably similar less obvious issues would correct quickly with tryptophan. In the US, where B vitamins are routinely supplemented, it is possible to have tryptophan deficiency without niacin deficiency. Copper effects due to enzyme mis-metalization or mitochondrial deficiency could be vague and of unknown delay.

Table I shows some dosing ideas for nominally healthy adult humans based on literature values, theory, and scaled amounts from dog feeding.

Material	RDA	Human NOAEL	Amount/Dose	Dosing	Comments
L-Tryptophan	250-425mg/day [174]	4.5g/d[57]	200mg	2-3/day	powder floats, mix with oil or emulsifier
L-Tyrosine	100mg/kg/day [63]		400mg	2-3/day	may be reactive, avoid with copper, may need more with dark hair or skin
	4-6g/day [201]				for PAH deficiency
L-Arginine		30g/day [38]	400mg	2-3/day	may also need lysine hours apart
K1			5-10mg	3/day	1% powder, avoid light, include emulsifier
K2, MK-4 + MK-7			15mg	daily	15mg capsules, avoid light , include emulsifier
Vitamin K	0.065-.12mg/day [180]				all sources of vitamin K
Copper	.9-1.2mg/day [35]	10mg/day [206]	5-10mg[148]	daily	citrate or glycinate, may also require zinc or have other issues with chronic higher doses
Citric acid		1200mg/kg/day [48]	3g/day[a]	multiple	available in bulk as a spice online, in diet drinks and juice. May demineralize teeth at low pH, consider swallowed capsules.

[a] this is total for the day as opposed to other quantities

TABLE I: Baseline human dosing estimates based on limited personal experience with self and dogs scaled roughly by weight. NOAEL's are literature values for healthy adults from the indicated source. RDA's change with time and vary among sources. Tryptophan powder will not wet easily, mix with emulsifier pantothenate although there is reaction potential For home use, note that a quater teaspoon is about 1.25 cc and ingredientr densities may vary between about .2-2 gram/cc or so. Calibration of volume measures with an accurate milligram scale may be required for bulk products.

6. CONCLUSIONS

The lack of an obvious or proven safe and effective approach to the covid-19 suggests that some exploratory work in less accepted areas may be informative if not useful. Currently published analyses have ignored things like protein C and neopterin as well as larger issues with nutrient status creating much uncertainty about the disease. The age distribution suggests that the virus is aided by attributes that segregate with age. My current work points to specific nutriotional features of old age that make good candidates for testable and informative interventions. Most of these could be easy to explore safely even in an amateur informal setting. Some may be considered reasonably safe but others like vitamin K may be more controversial. Any information obtained on these in the disease setting may be informative about the SARS-Cov-2 and aging vulnerabilities too. It is not just the lack of nutrient intake that may need to be corrected but also the distribution depending on ultimate bottlenecks in defective or competing transporters or metabolic pathways. Details matter and just mixing together nutrients is no assurance that any benefits will be realized. Physical properties and interactions need to be considered and some nutrients may even need to be limited to see benefits from those of interest. If these approaches work against the SARS-Cov-2 with more careful control , they may be modified to also mitigate age related diseases.

7. SUPPLEMENTAL INFORMATION

7.1. Computer code

8. BIBLIOGRAPHY

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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 as the original goal was to optimize feeding for dogs with various conditions. 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. I have no interest in the makers of any of the products named in this work.

Appendix B: About the author

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 (BSEE 1984, MSEE 1985) 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
AFIB	Atrial FIBrillation
BH4	Tetrahydrobiopterin
COPD	Chronic obstructive pulmonary disease
CMV	Cytomegalovirus
DIC	Disseminated Intravascular Coagulation
EET	Eosinophil Extracellular Trap
ERGIC	Endoplasmic Reticulum - Golgi intermediate compartment
IBD	Inflammatory Bowel Disease
IDO	Indoleamine Dioxygenase
NET	Neutrotphil Extracellular Trap
NAFLD	Non Alcoholic Fatty Liver Disease
NOAEL	No Observed Adverse Event Level
PAH	Phenylalanine Hydroxylase
RDA	Recommended Daily Allowance
RDI	Recommended Daily Intake
SVZ	Subventricular zone
VKDP	Vitamin K dependent proteins
VKOR	Vitamin K oxidio reducatase

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 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 reviwed 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-2020-002-0.10 .

Version	Date	Comments
0.01	2020-05-11	Create from empty.tex template
0.10	2020-07-01	NOTES version for discussion
-	July 1, 2020	version 0.10 MJM-2020-002-0.10
1.0	20xx-xx-xx	First revision for distribution

Released versions,

Version	Date	
0.10	2020-07-01	https://media-exp1.licdn.com/dms/document/C4E1FAQGHDj69cUckbw/feedshare-document-pdf-analyzed/0?e=15
0.10	2020-07-01	https://www.linkedin.com/posts/marchywka_notes-on-agin

Suggested Bibtex:
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VERSION = { 0.10 July 1, 2020 PUBLIC NOTES },
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ADDRESS = {306 Charles Cox , Canton GA 30115},
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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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