Review Article

Magnesium and Longevity

Patrick Chambers[1]

1. Torrance Memorial Medical Center, Torrance, United States

Magnesium (Mg) is not prominent among the list of well known anti-aging agents. Yet the signs and symptoms of aging mimic those of Mg deficiency. Mg is required for over 800 enzymatic reactions (as of 2022). This review does not correlate Mg status with clinical data on agents linked to longevity. The approach is physiologic and highlights specific Mg dependent reactions required by these longevity linked biomarkers. Many of these share common pathways to extend healthspan. Mg is a required cofactor in the synthesis of vitamin D and melatonin and activation of six of the eight B vitamins. It is a required cofactor for all CYP450 enzymes. It is directly responsible for the appropriate methylation of proteins and DNA, which control the epigenome. The MTHFR (methylenetetrahydrofolate reductase) 677T allele that compromises methylation is present in a majority of Americans. Aberrant methylation predicts the severity of Covid-19 and its persistence into long Covid. Mg is a silent benefactor that may indirectly link these longevity agents, but only if viewed in context with calcium (Ca), i.e., Ca:Mg. Both compete for the same receptor. To fully exploit these longevity agents sufficient Mg is required. The pertinent physiology is presented.

Correspondence: papers@team.qeios.com — Qeios will forward to the authors

1. Introduction

Optimal longevity involves extending healthspan, not just lifespan. Its pursuit has been energized by recent breakthroughs in our understanding of its pathobiology. The contribution of the gut microbiome to our general health is at the top of this list. Many elements are associated with longevity. Some are well known, e.g., high density lipoprotein cholesterol (HDL-C), heart rate variability (HRV), vitamin D, and telomeres. Others are less well known but well documented, e.g., aryl hydrocarbon receptors (AhRs), histone deacetylase inhibitors (HDACi). There are numerous molecules associated with longevity. Popular ones include short chain fatty acids (SCFAs), polyunsaturated fatty acids, and glucagon-like peptide-1

(GLP-1). Ozempic (semaglutide) is a GLP-1 agonist. Although well known for weight loss, it also brings longevity benefits. Almost all exhibit some connection to the gut microbiome. Many involve the epigenome and raise the question - can we control our genes to some extent by what we eat? Intake of Mg is critical. It is a requirement for over 800 enzymatic reactions[1], not just the frequently quoted 300 enzymatic reactions. It is involved in over 80% of known metabolic functions[2]. The dominance of so many Mg dependent enzymes may in part explain why many Mg deficiency symptoms mimic those of aging[3]. Mg deficiency has long been connected to cellular senescence[4]. Mg potentiates each of the discussed longevity agents, either directly or indirectly by enhancing the precursors or metabolites of their designated biopathways. Half of Americans are deficient in Mg. This figure would be much higher if the lower limit of its acceptable range were to be slightly increased to eliminate normomagnesemia Mg deficiency, as indicated by intra-erythrocytic Mg[5], now known as chronic latent Mg deficit.

2. Discussion

I. Gut Microbiome

A healthy gut microbiome produces abundant longevity agents - secondary bile acids, indoles, and short chain fatty acids[6]. Each triggers secretion of GLP-1[7]. GLP-1 agonists are also linked to longevity[8][9], primarily because they preserve insulin sensitivity. This biomarker deteriorates with age, even in those with normal blood glucose and body weight[10]. Insulin resistance is an early hallmark of cancer, type 2 diabetes (T2DM), and dementia (T3DM)

A. Secondary Bile Acids

Primary bile acids are normally conjugated in the liver after hepatic degradation of cholesterol. This involves CYP450 enzymes, which are all Mg dependent[11]. These primary bile acids must be deconjugated before gut bacteria can dehydroxylate and dehydrogenate them to produce secondary bile acids[12]. A central pathway in the production of secondary bile acids by gut bacteria is 7-alpha dehydroxylation[13]. 7-dehydroxylated bile acids are the most potent agonists for host bile acid receptors[14]. This makes the subsequent 7-alpha dehydrogenation equally significant. This latter reaction is significantly enhanced by Mg[15]. The contribution of Mg to production of secondary bile acids is, therefore, operating in both the liver (CYP 450 enzymes) and the intestinal lumen (7-alpha dehydrogenase)

Gilbert's syndrome, linked to longevity, is a genetic disorder characterized by an increase in unconjugated bilirubin[16]. It is characterized by less oxidative stress, less inflammaging, lower body mass index, stronger vagal tone and less risk for cardiovascular disease (CVD) or T2DM than healthy controls[17]. The longevity benefits in Gilbert's Syndrome might be due to the fast tracking of unconjugated primary bile acids to secondary bile acids. Unconjugated primary bile acids normally compose less than 1% of total biliary acids[18]. Nonetheless, production of primary bile acids is critical and Mg deficiency compromises this. Bile acid production decreases with age[19], as do Mg levels. Indeed the symptoms of Mg deficiency reflect those of aging[3].

B. Indoles

The gut microbiome also produces indole/indole derivatives, longevity agents that also trigger release of GLP-1. Gut bacteria metabolize tryptophan, creating these indole derivatives. Down regulation of tryptophan dioxygenase (TDO) and indoleamine dioxygenase (IDO) increases tryptophan and decreases kynurenine, extending lifespan[20] (see figure 1).

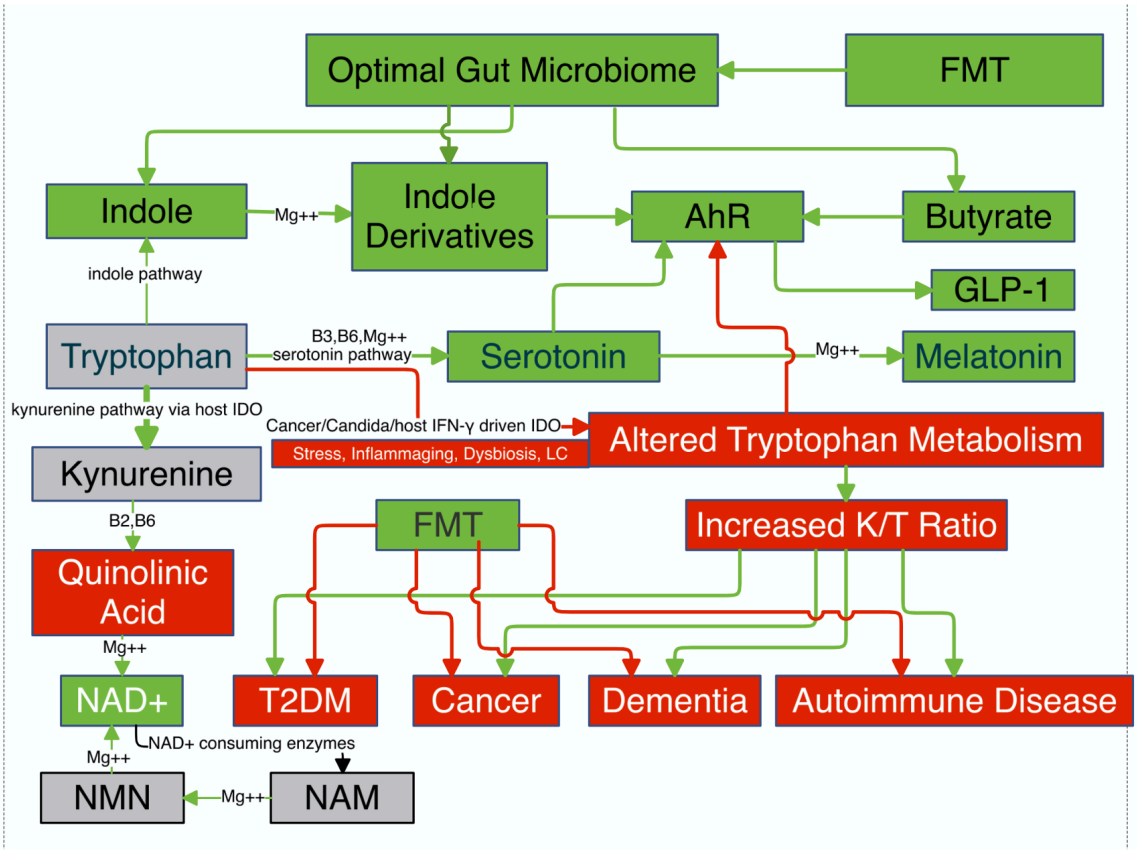

Figure 1. AhR=aryl hydrocarbon receptor, LC=long Covid, FMT=fecal microbiota transplantation, K/T=kynurenine to tryptophan, T2DM=type 2 diabetes, GLP=glucagon like peptide, NAD=nicotinamide adenine dinucleotide, red arrows, boxes => unfavorable, green arrows, boxes => favorable

Altered tryptophan metabolism (ATM) and increased kynurenine to tryptophan ratio are hallmarks of cancer, dementia, autoimmune disease, and obesity. In each tryptophan depletion is prominent, leaving less for indole synthesis. Indole derivative production also requires CYP 450 enzymes, all of which are Mg++ dependent[11]. Indoles also induce the release of GLP-1, known to suppress appetite, increase insulin secretion and slow gastric emptying[8]. Indoles are also ligands for aryl hydrocarbon receptors (see section IV), another longevity agent conduit.

C. Butyrate

Butyrate is another GLP-1 agonist[21] and an aryl hydrocarbon ligand. Both are longevity indicators. Probiotics, rich in butyrogenic bacteria, are associated with longevity[22] and Mg enhances probiotic efficacy[23]. Butyrate produced by gut bacteria via vagal afferents may improve HRV[24][25]. Candida and

cancer cells are prominent secretagogues for HDAC[26][27]. Butyrate is an HDACi[28] and may also mediate the efficacy of calorie restriction in enhancing longevity[29]. Gut microbiota cannot produce SCFAs in the absence of Mg[30]. Omega 3 fish oils upregulate SCFA production, especially butyrate[31] and enhance biodiversity[32].

II. Vitamin D

Vitamin D is another well recognized longevity agent[33] and Mg is critical to its synthesis[34]. The active forms of vitamin B2 (FAD) and B3 (NAD), required for the synthesis of the D3 precursor, 7-dehydrocholesterol, are also Mg dependent (see figure 2).

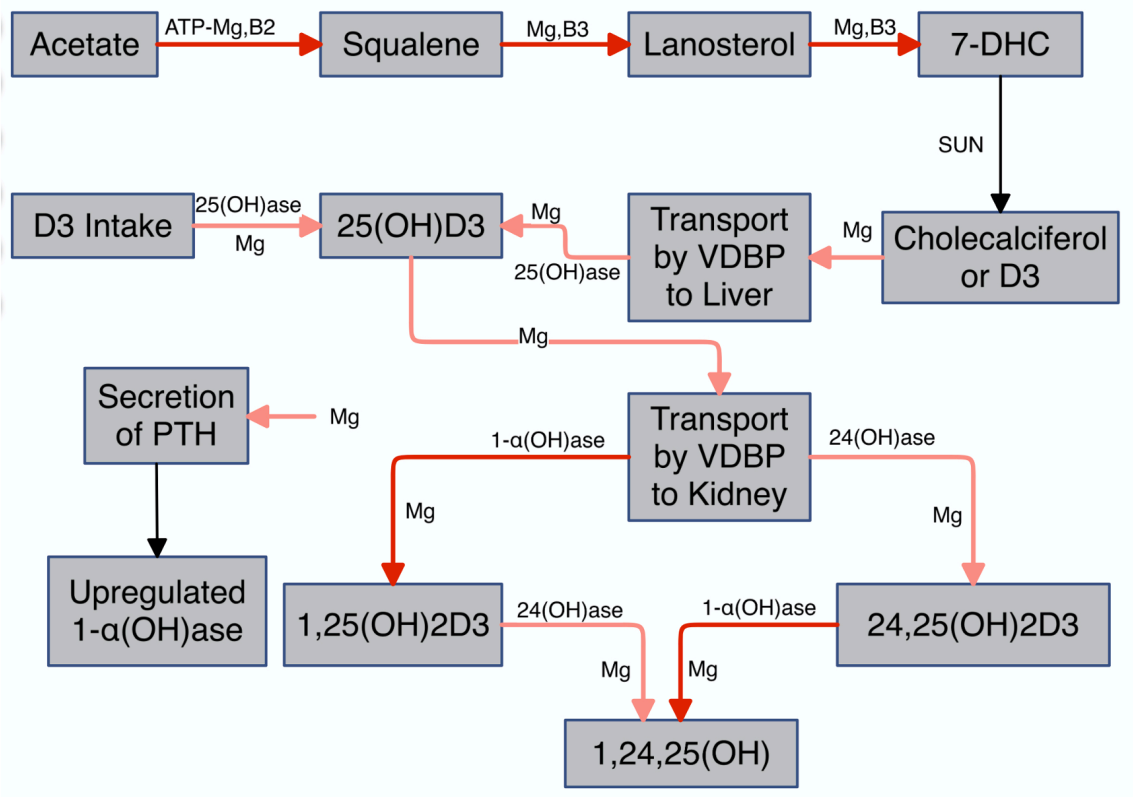

Figure 2. This sterol biosynthetic pathway for cholecalciferol decreases with age and is further challenged by Mg deficiency. Intensity of red arrows indicates the impact of Mg deficiency. DHC=dehydrocholesterol, PTH=parathormone, VDBP=vitamin D binding protein, D3=cholecalciferol

Vitamin D efficacy in longevity is linked to its healthful effects on methylation and the epigenome[35]. Vitamin D supplementation reduces total cholesterol, low density lipoprotein (LDL) cholesterol, and

triglyceride levels but not HDL-C levels[36] (see section V). Vitamin D reversibly improves the gut microbiome[37]. D3 directly inhibits Candida hyphal morphogenesis. Candida can produce its own IDO, which depletes tryptophan, upregulates the kynurenine pathway, and alters tryptophan metabolism (ATM)[38].

III. Telomeres

The link between telomere length and mortality, like HDL-C (section VI), may be U shape. Initially telomere length was reported as positively linked to longevity. However, recently this has been challenged. Long telomeres may be associated with cancers[39]. Telomeres shorten with age (attrition) and longevity is characterized by less telomere attrition, i.e., longer telomeres v those less long lived[40]. This shortening is due to loss of telomere homeostasis with cellular senescence. Mg maintains telomere homeostasis[41]. Anti-aging agents and conditions that delay telomere shortening include vitamin D[42], dietary Mg[43], calorie restriction[44], and GLP-1[45]. Telomere attrition is influenced by oxidative stress, inflammation, insulin resistance, and hyperglycemia, well controlled by GLP-1[46]. Gilbert's Syndrome also manifests less telomere attrition[47]. Regulation of telomerase and telomere homeostasis is subject to epigenetic control and DNA methylation[48] (see section VIII).

IV. AhR

Recently the vital role of aryl hydrocarbon receptors (AhRs) in aging[49], dementia, autoimmune disease, cancer[50], and ASCVD[51] has been recognized. AhR activity is dependent on its ligands. Kynurenines are AhR ligands that accelerate aging and neurodegeneration, while butyrates and indoles of intestinal bacterial origin are AhR ligands that oppose this[49] and promote longevity. ATM inactivates the immune response dependent function of AhR[52]. Not only are indoles and butyrate AhR ligands[53], but subsequent AhR activation induces cytochrome CYP450 enzymes that facilitate gut absorption of indoles[54]. All CYP450 enzymes are Mg dependent[11]. Indole derivatives also stimulate butyrate-producing gram-positive bacteria[54].

V. HDL-C

HDL-C has long been linked to longevity[55]. However, more recent studies report that the HDL-CVD relationship is U-shape, i.e., low and extremely high HDL-C levels can entail health risks[56]. Mechanisms

underlying this non-linear relationship are presently unknown. However, one study suggests that the capacity of HDL to acquire free cholesterol during triglyceride-rich lipoprotein (TGRL) lipolysis by lipoprotein lipase underlies the non-linear relationship between HDL-C and cardiovascular risk[57]. Lipoprotein lipase (LPL) induced lipolysis removes blood triglycerides. Elevated triglycerides directly compromise the ability of HDL to clear cholesterol, as HDL-C increases above 100 mg/dL. This creates a scenario of elevated but ineffectual HDL-C in a triglyceride rich environment, hypothetically explaining the increase in CVD despite extremely high HDL-C. LPL mediated lipolysis is the rate-limiting step in the removal of triglyceride from the bloodstream[58] and also regulates HDL-C. LPL is Mg dependent[59]. Perhaps a Mg shortfall and its consequent impact on rate limiting LPL contribute to the increase in CVD, despite high HDL-C. Might Mg deficiency compromise the efficacy of elevated HDL just as it compromises the efficacy of vitamin D3?

VI. HRV

Serum HDL-C levels correlate with high frequency HRV indices[60]. Low total cholesterol and LDL-C were significantly associated with low frequency HRV indices[61]. Not surprisingly HRV is another well recognized longevity agent[62].

It can predict disease well before symptoms appear[63] and directly reflects vagal tone[64]. Anti-aging butyrate suppresses food intake via vagal signals to the brain[65].

Calorie restriction also improves HRV[66]. The impact of HRV and calorie restriction on longevity suggest that the appetite suppressing properties of butyrogenic gut bacteria via vagal afferents may increase HRV. This has recently been reported[67]. Mg level is positively related to HRV, while Ca/Mg ratio is negatively related to HRV[68]. Vitamins D and B-12 deficiencies are associated with reduced HRV[69]. The active forms of both are Mg dependent.

VII. Melatonin, Resveratrol, Vitamin C, Tryptophan, Calorie Restriction, α-Ketoglutarate, Methionine Restriction, and Lactate Dehydrogenase

Two popular decades old anti-aging supplements are melatonin and resveratrol. Melatonin can be sourced endogenously from the pineal gland or exogenously. Its synthesis from tryptophan is Mg dependent (see figure 1). Melatonin opposes CVD and neurodegenerative disease with antioxidant and anti-inflammatory properties[70].

Many of the healthful benefits of resveratrol are mediated by Mg dependent enzymes, e.g., protein and nucleotide kinases. This enables resveratrol to function as anti cancer, antioxidant, anti obesity, anti-dementia, anti-T2DM, and anti CVD[71]. Moreover, resveratrol and quercetin, proven to extend lifespan, are compounds that can also serve as AhR ligands[72].

Mg enhances the anti cancer property of Vitamin C via SCVT (sodium coupled vitamin C transporter)[73] [74]. Tryptophan has recently emerged as a longevity agent[75]. It opposes the hyphal morphogenesis of Candida[76], associated with decreased healthspan[77]. ATM is characterized by tryptophan depletion and increased K/T ratio and is associated with cancer, dementia, autoimmune disease, and T2DM[78].

Alpha-ketoglutarate is another recently discovered longevity agent, prominent in the Krebs cycle. Its longevity property mimics calorie restriction via dietary restriction and inhibition of ATP synthase[79]. However, Mg enhances the efficacy of calorie restriction[80] and probably α-KG as well. Both depress oxidative stress. In addition the enzymes responsible for the synthesis of α-KG and glutamine from glutamate are both Mg dependent. Any Mg deficiency may increase glutamate, an anti-aging and dementia promoting agent[81].

Methionine restriction (MR) also possesses longevity properties also via a mechanism similar to that of calorie restriction[82]. These include anti-cancer, anti-aging, anti-inflammatory, and anti-obesity[83]. The benefits of MR may be due to reduced oxidative stress and redox status changes through mechanisms not yet discovered[82]. Five of ten enzymes in the Krebs Cycle (not including pyruvate dehydrogenase) are dehydrogenases (Mg dependent). These are mitochondrial electron transfer reactions (redox reactions) that also require magnesium dependent B2 as flavin adenine dinucleotide (FAD) and B3 as niacinamide adenine dinucleotide (NAD). MR longevity benefits may be due to a reduction in free radical leakage from mitochondria[82]. B2 and B3 protect mitochondria from oxidative stress, e.g., transsulfuration pathway and glutathione synthesis[84] (see figure 3). Consequently any Mg shortfall will curtail longevity benefits of MR. It will curtail production of glutathione, the most powerful human antioxidant (see figure 3).

Not surprisingly another Mg dependent dehydrogenase, lactate dehydrogenase (LDH), is a longevity biomarker, albeit an inverse one[85]. It converts lactic acid to pyruvate, its most critical function[86]. While blood lactate is bad, gut lactate is good. During exercise blood lactate can enter the gut and feed butyrogenic bacteria[87].

Lactogenic bacteria, e.g., Bifidobacteria and Lactobacilli, can also crossfeed butyrogenic bacteria, e.g., Faecalibacterium and Roseburia[88] and lower host lactate levels[89]. Elevated levels of lactate and LDH are linked to cancer (Warburg effect), CVD, dementia, and chronic inflammatory diseases, including Covid-19[90].

VIII. Methylation

Methylation of certain CpG islands (cytosine paired with guanine) in the DNA epigenome promotes or not the expression of other genes. Aberrant DNA methylation predicts aging[91][92][93]. Aberrant methylation enhances risks for cancer, dementia, and autoimmune disease[94]. This promotion/suppression mechanism for the epigenome occurs through transfer of methyl groups from SAMe to DNA and proteins (see figure 3). Aberrancy arises when this transfer is compromised. Methylation is compromised by the 677T MTHFR allele, present in most Americans[95], and certain vitamin B deficiencies (see figure 3). B9 (folate) and B12 (cobalamin), critical to both the folic acid cycle and the methionine cycle, require methylation for activation. Heterozygous 677T reduces MTHFR activity by 35%, while the homozygous state reduces MTHFR activity by 70%[96]. B2 and B3 are FAD and NAD dependent respectively. Dinucleotides contain two phosphates, incorporation of which requires two ATP-Mg^{++} molecules. To convert inactive B6 (pyridoxine) to its active form (pyridoxal phosphate) also requires phosphorylation (ATP-Mg^{++}). Therefore, any Mg deficiency further compromises optimal DNA methylation and accelerates aging.

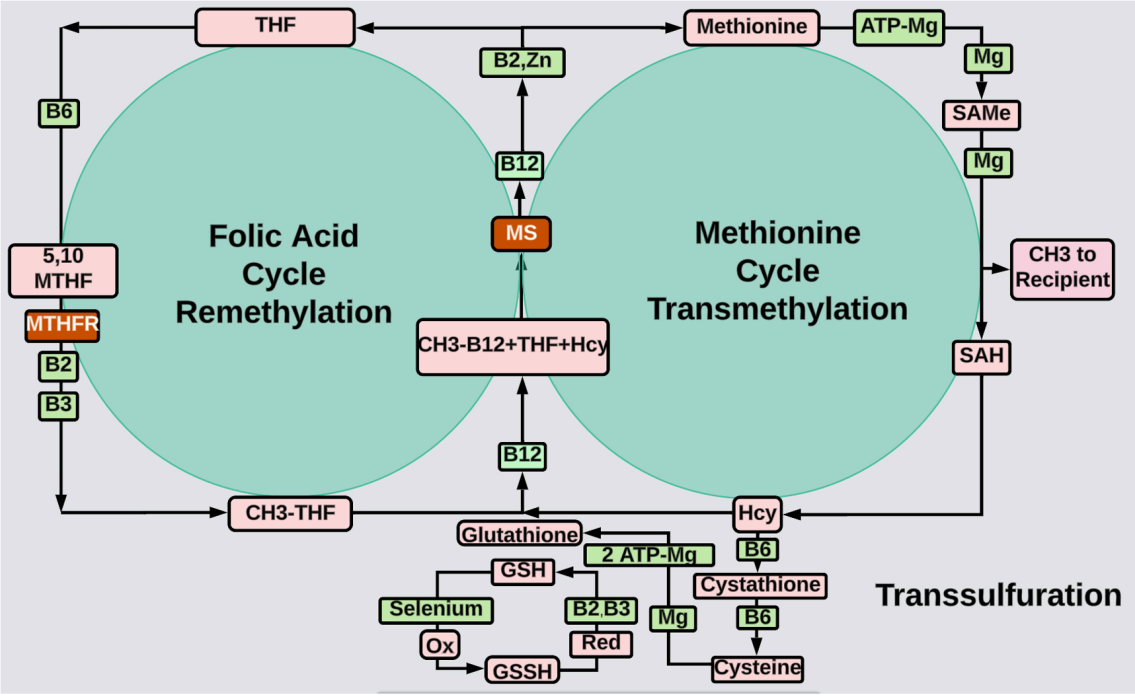

Figure 3. Methylation is the primary promoter/suppressor mechanism for the epigenome. Pink boxes are molecules, green boxes are required cofactors, and red boxes are critical enzymes. MTHFR=methylenetetrahydrofolate reductase, THF=tetrahydrofolare, SAMe=S-adenosyl methionine, SAH=S-adenosyl homocysteine, Hcy=homocysteine, GSH=reduced glutathione, GSSH=oxidized glutathione

IX. Magnesium

Mg deficiency has been directly linked to aging[97]. It clearly potentiates directly or indirectly many recognized longevity agents. However, it also stands alone as a longevity agent itself, both with respect to biochemistry and to the gut microbiome. Seven of nine enzymes in the glycolytic pathway are Mg dependent. In the Krebs cycle seven of 10 enzymes are Mg dependent. Mg deficiency negatively impacts ATP production and increases oxidative stress. Mg deficiency is linked to insulin resistance, an early hallmark of cancer, T2DM, and T3DM. Mg is critical to the kynurenine pathway (see figure 1) and production of NAD+. ATM characterizes cancer, dementia, autoimmune disease, and T2DM[78]. Mg dependent phosphoribosyl transferases and adenylyl transferases, key enzymes determining aging[98], convert quinolinic acid (neurotoxic) to NAD+ and nicotinamide adenine mononucleotide (NAM) to NAD+ respectively (see figure 1). NAD+ decreases with age[99], while Mg deficiency increases with age[4]. Thus,

doi.org/10.32388/N1SCBR.2

Mg deficiency compromises the ability to recycle NAD+, enhancing risks due to stress, inflammaging, disease, and dysbiosis.

ATM is linked to gut dysbiosis[100], which is linked to the gut microbiome[101]. Mg status is also directly linked to gut microbiota. A Mg-deficient diet reduces the abundance of Bifidobacterium. A Mg rich diet increases both biodiversity and the abundance of Bifidobacterium[102]. The Mediterranean diet, rich in Mg, enhances biodiversity and growth of lactobacilli and bifidobacteria[103]. Lactobacillus spp. can significantly increase the bioavailability of magnesium[102]. These lactogenic bacteria (lactobacilli and bifidobacteria) then crossfeed butyrogenic bacteria, increasing butyrate, an emerging longevity agent (see section IC). The gut microbiome of centenarians exhibits increased activity in the phosphatidyl-inositol pathway and glycosphingolipid biosynthesis[104]. The phosphatidyl-inositol pathway starts with the magnesium dependent conversion of glucose to glucose-6-phosphate. Subsequent pathway steps are also heavily dependent on ATP and cAMP, both of which are Mg dependent. Glycosphingolipid biosynthesis involves glycosyltransferases and glucosidases. Most glycosyltransferases are Mg dependent and some glucosidases are Mg dependent, e.g., some β-glucosidases[105]. The gut microbiome of the younger elderly shows decreased saccharolytic capacity aka glucose metabolism and low levels of SCFAs, tryptophan, indole, and nicotinamide[104]. All of these are longevity agents and have been discussed in depth. Yet awareness of Mg deficiency has always been subordinate to that of Ca, e.g., routine chem panels offer Ca but not Mg. Few realize that they are antagonists. Ca:Mg is rarely mentioned.

A. Ca:Mg

The calcium sensing receptor (CaSR) is a Mg dependent G protein coupled receptor activated by Ca^{++} or Mg^{++}[106][107]. Most of the focus between Mg and vitamin D pertains to the criticality of Mg in the synthesis of the sunshine vitamin. But vitamin D improves the absorption of not only Ca but also Mg, although to a lesser extent[108]. The active forms of Ca and Mg are their cations (Ca^{++}, Mg^{++}). Both bind to the CaSR and excess Ca^{++} can competitively inhibit Mg^{++}. In the Western diet Ca outweighs Mg. According to NHANES (National Health and Nutrition Examination Surveys) the mean dietary intake of Ca:Mg for Americans has escalated from 2.6 in 1977 to over 3.0 since 2000. Between 1977 and 2012, US Ca intake increased at a rate 2 - 2.5 times that of Mg[109]. In1989 Jean Durlach, founder of the International Society for Development of Research on Magnesium, reported that 2.0 was the proper target ratio (circulating cation concentrations in mM). An elevated Ca:Mg ratio is characteristic of cancer,

autoimmune disease[110] and ASCVD[111] and this ratio should be maintained between 1.7 and 2.8[109]. The Oriental diet is typically low in Ca, while the Occidental diet is typically low in Mg[112]. This Ca:Mg imbalance is often overlooked, because a) Mg is not usually included in any lab chemistry panel, b) lower limit on the "normal" range may be too low, c) serum Mg (bound and free) does not reflect Mg^{++}. The median intake of Mg is insufficient to fully exploit the healthful benefits of vitamin D, especially for CVD and colon cancer[113]. This suggests that the lower limit of "normal" lab serum Mg^{++} values (.75-.95 mM), determined by extensive sampling from this large "healthy" population (50% are deficient), is too low. Several studies have suggested.85 mM, as a lower limit[114][115]. Yet lab range values for serum Mg^{++} in healthy controls remain unchanged, despite repeated alerts over the past two dozen years[116][117][118]. Another study of 91 participants found that a detailed diet questionnaire predicted suboptimal Mg status in 100%, yet lab testing confirmed this in only 76%[119]. Might this also challenge the validity of.75 mM as a lower limit? This gray zone between.75 and.85 may correspond to low intra-erythrocytic Mg when serum Mg is within normal limits. Initially termed normomagnesemia Mg deficiency[5], it is now known as chronic latent Mg deficit. This has been demonstrated for migraines and PMS[5].

Calculation of serum Mg^{++} in "healthy" individuals with normal renal function, with midrange serum albumin, and without medications can most likely be determined from serum Mg (bound and unbound). If one compares the normal ranges for serum Mg and Ca with the normal ranges for ionized Mg and Ca, they align exactly, but only if Mg^{++} and Ca^{++} represent 70% and 50% of total serum levels respectively. When the midpoints of the ranges for the ionized forms (Ca^{++} = 1.2 mM, Mg^{++} =.6 mM) is determined, the Ca:Mg is 2.0, very much in line with Durlach's recommendation.

This means that if the lower limit of normal for serum Mg were to be raised to.85 mM (2.0 mg/dL), then to maintain this recommended ratio the lower limit of normal for serum Ca should be raised to ~2.4 mM (9.5 mg/dL). This increase in the lower limit of normal Ca in addition to Mg seems appropriate. According to the NIH, data from NHANES 2009-2010 indicated that 42% of Americans did not meet their Estimated Average Requirements for Ca as recommended by the Institute of Medicine[120]. The prevalence of Ca deficiency is even greater in low and middle income countries[121].

B. Magnesium and Covid-19

Ca:Mg > 5.0 is strongly associated with Covid-19 mortality[122]. Mg levels directly correlate with Covid-19 disease for risk of hospitalization, length of stay, mortality, and long Covid[123]. Ca:Mg might even further

refine this link with severity. Among individuals less than 65 y with Ca:Mg > 2.6, reducing the ratio to around 2.3 downregulated the TMPRSS2 gene. Decreasing Ca:Mg improved methylation and ameliorated or prevented Covid-19[124]. Aberrant methylation is not only a biomarker for Covid-19 but also for long Covid[125]. This suggests that those with the 677T MTHFR variant allele (half of Americans) are at greater risk, as has been reported[126].

ACE2 receptor bearing cells are targeted and lysed by SARS CoV2. Intestinal epithelial cells are rich in ACE2 receptors. This is problematic because these receptors must complex with B^0ATs (neutral or nonpolar amino acid transporters) to enable absorption of tryptophan. Tryptophan, a longevity agent, opposes Candida hyphal morphogenesis[76]. Candida produces its own IDO[76] that competes with host IDO and drives ATM[38] (see figure 1).

In summary, the dozen or so longevity agents evaluated in this review appear to be linked to Mg, either directly in the synthesis of the agent or indirectly along the relevant metabolic pathway. Although the magnitude of their impact in any individual is complex and impossible to quantitate, their limited presence in those on a Western diet or lifestyle is difficult to deny. Additional longevity agents may yet be discovered, expanding options in our quest for longevity. Figure 4 illustrates their interlinkage.

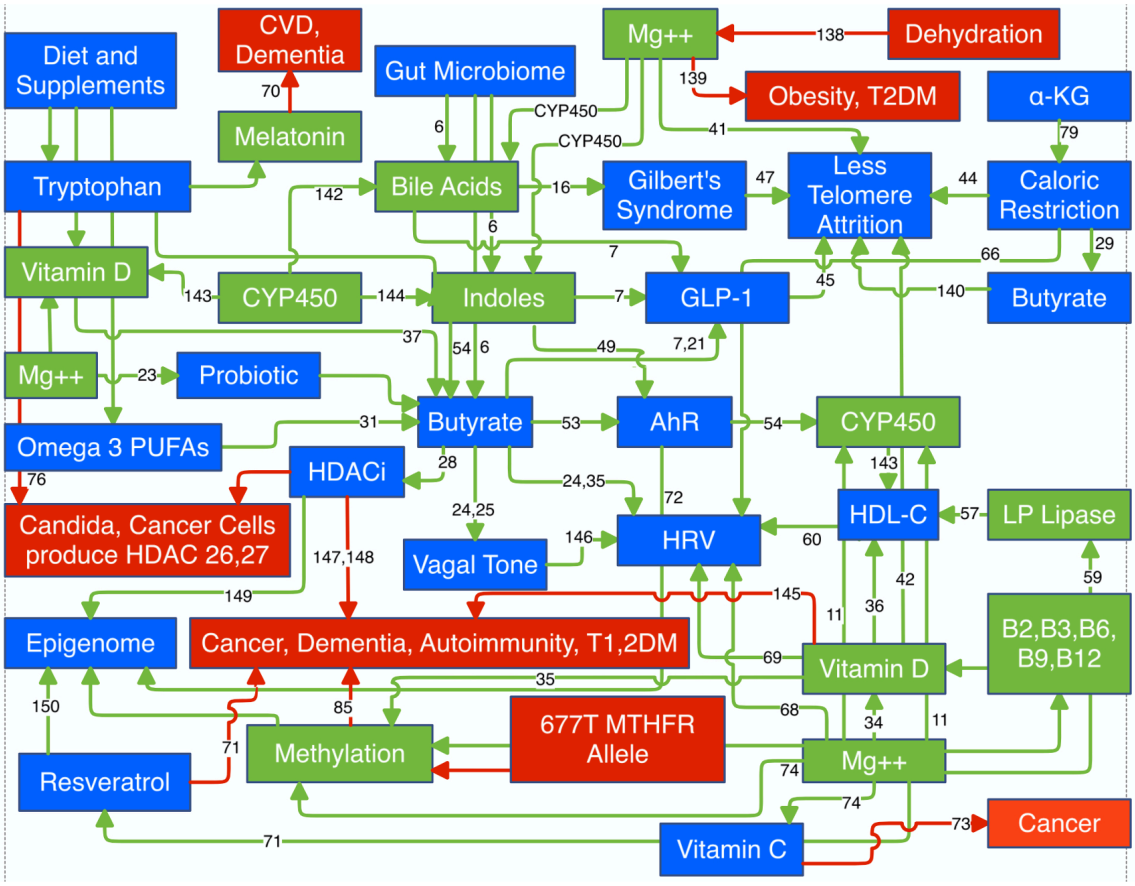

Figure 4. All blue boxes are directly associated with longevity. Green boxes are Mg++ dependent. Red boxes are anti-longevity. Green arrows promote and red arrows inhibit. PUFAs=polyunsaturated fatty acids, HDAC=histone deacetylase, GLP=glucagon like peptide, CYP=cytochrome P, AhR=aryl hydrocarbon receptor, HRV=heart rate variability, HDL-C= high density lipoprotein cholesterol, LP=lipoprotein

C. Therapeutic Interventions

The first step in addressing a potential Mg shortage is to assess Ca:Mg. If greater than 2.6, then efforts must be directed to lowering oral intake of Ca. Otherwise, increasing oral Mg will lower PTH and suppress Mg absorption. Administering a variety of Mg chelates, e.g., glycinate, maleate, taurate, threonate, also enhances absorption. Bowel tolerance should be the limiting factor and should be approached slowly. Mg citrate is especially noted for its laxative side effect. Combining oral intake of Mg with vitamin D is also helpful.

Mg bioavailability is increased by concomitant intake of the active form of vitamin B, pyridoxal phosphate (PLP)[127]. PLP, but not pyridoxine, appears to form a complex with Mg and hence may

enhance the transport or accumulation of Mg in cells[128]. However, several old and recent articles have challenged this beneficial effect of B6 on Mg absorption[129][130], but both employed Magne, which is 300 mg Mg and 30 mg pyridoxine. Another article claimed that B6 enhances erythrocytic Mg but only at high doses and that high doses risk peripheral neuropathy. This study also used Magne[131].

Even the NIH in its Aug 2023 update on B6 failed to acknowledge the efficacy differential between pyridoxine and PLP. Furthermore, taking P5P concomitantly with Mg can potentially double[127] or triple[128] the absorption of Mg. Not only does PLP enhance cellular uptake of Mg but Mg enhances that of PLP[132]. B6 as pyridoxine, the inactive form and the most common form in B supplements, competitively inhibits P5P, the active form, and can cause peripheral neuropathy[133]. B2 as FAD is a Mg dependent and required cofactor for the synthesis of PLP. This means that if B2 is deficient without PLP supplementation, then B6 supplementation as pyridoxine can cause symptoms of B6 deficiency. Synthesis of PLP is also Mg dependent.

Not surprisingly B vitamins are linked to longevity[134]. Of the eight, six require Mg to attain activated status. B1 as thiamine pyrophosphate, B2 as FAD, B3 as NAD, and B6 as pyridoxal phosphate require phosphorylation. B9 and B12 require methylation. All phosphorylation and methylation reactions require Mg. All five of these B vitamins are critical to methylation (see figure 3). The value of a prebiotic, e.g., sauerkraut, kimchi, D-mannose, probiotic, e.g., yogurt, and postbiotic, e.g., butyrate, in the quest for a better gut microbiome and healthful longevity cannot be underestimated. Fecal microbiota transplantation has shown significant efficacy in treating cancer[135], autoimmune disease[136], and dementia[137]. This suggests that it is never too late to upgrade your gut microbiome in any therapeutic approach to disease, much less any preventative one (see figure 4).

3. Conclusion

Bile acids and HDL-C are longevity agents that necessitate hepatic metabolism by magnesium dependent CYP450 enzymes. Production of indoles by gut bacteria also require magnesium dependent CYP450 enzymes. Syntheses of the active forms of vitamins D, B1, B2, B3, B6, B9, and B12 are magnesium dependent. These activated B vitamins and Mg^{++} are all required cofactors in the remethylation (folate) and transmethylation (methionine) cycles, critical to the epigenome. Any shortfall in Mg status will weaken methylation and exacerbate the significant health problems associated with the MTHFR 677T variant allele, present in the majority of Americans (see figure 3). Aberrant methylation compromises the

immune response to SARS CoV2 and increases risk for long Covid. Mg actively suppresses obesity and T2DM. The longevity properties of Mg are highly dependent on Ca:Mg, rarely mentioned in contrarian reviews on the benefits of vitamin D or Mg supplementation. Compromised recycling of NAD+ due to Mg deficiency (see figure 1) and upregulation of IDO by cancer cells, Candida, and host IFN-gamma drive ATM, linked to cancer, dementia, autoimmune disease, T2DM, oxidative stress, inflammaging, and dysbiosis are all opposed by a healthy gut microbiome. Magnesium potentiates the healthful benefits of the gut microbiome and vice versa. Health problems related to normomagnesemia Mg deficiency, e.g., migraines and premenstrual syndrome, challenge the validity of the accepted lower limit for serum Mg. Although the discussed biochemistry and physiology are generally accepted, convincing clinical data, adjusted for D3 and Ca status, supporting the underappreciated role of Mg in longevity awaits.

> "Every known illness is associated with a magnesium deficiency,"
>
> Norman Shealy, Father of Holistic Medicine

Notes

The following references[138][139][140][141][142][143][144][145][146][147][148][149][150] appear only in Figure 4.

References

1. ^*Fiorentini D, Cappadone C, Farruggia G, Prata C. Magnesium: Biochemistry, Nutrition, Detection, and Social Impact of Diseases Linked to Its Deficiency. Nutrients. 2021 Mar 30;13(4):1136. https://doi.org/10.3390/nu13041136*
2. ^*Workinger JL, Doyle RP, Bortz J. Challenges in the Diagnosis of Magnesium Status. Nutrients. 2018 Sep 1;10(9):1202. https://doi.org/10.3390/nu10091202*
3. a, b*Dominguez LJ, Veronese N, Barbagallo M. Magnesium and the Hallmarks of Aging. Nutrients. 2024;16(4):496. https://doi.org/10.3390/nu16040496*
4. a, b*Killilea DW, Maier JA. A connection between magnesium deficiency and aging: new insights from cellular studies. Magnes Res. 2008 Jun;21(2):77-82. http://www.ncbi.nlm.nih.gov/pmc/articles/pmc2790427/*
5. a, b, c*Mansmann HC Jr. Consider Magnesium Homeostasis: II: Staging of Magnesium Deficiencies. Pediatric Allergy, Immunology and Pulmonology. 1993;7:211-215. https://doi.org/10.1089/pai.1993.7.211*
6. ^*Jin L, Shi L, Huang W. The role of bile acids in human aging. Med Rev (2021). 2024 Mar 7;4(2):154-157. https://doi.org/10.1515/mr-2024-0003*

7. ^Masse KE, Lu VB. Short-chain fatty acids, secondary bile acids and indoles: gut microbial metabolites with effects on enteroendocrine cell function and their potential as therapies for metabolic disease. Front Endocrinol (Lausanne). 2023 Jul 25;14:1169624. https://doi.org/10.3389/fendo.2023.1169624
8. a, bChavda VP, Balar PC, Vaghela DA, Dodiya P. Unlocking longevity with GLP-1: A key to turn back the clock? Maturitas. 2024 Aug;186:108028. https://doi.org/10.1016/j.maturitas.2024.108028
9. ^Peng W, Zhou R, Sun ZF, Long JW, Gong YQ. Novel Insights into the Roles and Mechanisms of GLP-1 Receptor Agonists against Aging-Related Diseases. Aging and disease. 2022;13(2):468-490. https://doi.org/10.14336%2FAD.2021.0928
10. ^Huang LY, Liu CH, Chen FY, Kuo CH, Pitrone P, Liu JS. Aging Affects Insulin Resistance, Insulin Secretion, and Glucose Effectiveness in Subjects with Normal Blood Glucose and Body Weight. Diagnostics (Basel). 2023 Jun 24;13(13):2158. https://doi.org/10.3390/diagnostics13132158
11. a, b, cMansmann HC Jr. Consider magnesium homeostasis: III: cytochrome P450 enzymes and drug toxicity. Applied Immunohistochemistry & Molecular Morphology. 1994;8:7-28. https://doi.org/10.1089/pai.1994.8.7
12. ^Fuchs CD, Trauner M. Role of bile acids and their receptors in gastrointestinal and hepatic pathophysiology. Nat Rev Gastroenterol Hepatol. 2022;19:432–450. https://doi.org/10.1038/s41575-021-00566-7
13. ^Wise JL, Cummings BP. The 7-α-dehydroxylation pathway: An integral component of gut bacterial bile acid metabolism and potential therapeutic target. Front Microbiol. 2023 Jan 9;13:1093420. https://doi.org/10.3389/fmicb.2022.1093420
14. ^Vico-Oton E, Volet C, Jacquemin N, et al. Strain-dependent induction of primary bile acid 7-dehydroxylation by cholic acid. BMC Microbiol. 2024;24:286. https://doi.org/10.1186/s12866-024-03433-y
15. ^Ji S, Pan Y, Zhu L, Tan J, Tang S, Yang Q, Zhang Z, Lou D, Wang B. A novel 7α-hydroxysteroid dehydrogenase: Magnesium ion significantly enhances its activity and thermostability. Int J Biol Macromol. 2021 Apr 30;177:111-118. https://doi.org/10.1016/j.ijbiomac.2021.02.082
16. ^Horsfall LJ, Nazareth I, Pereira SP, Petersen I. Gilbert's syndrome and the risk of death: a population-based cohort study. J Gastroenterol Hepatol. 2013 Oct;28(10):1643-7. https://doi.org/10.1111/jgh.12279
17. ^Wagner KH, Khoei NS, Hana CA, Doberer D, Marculescu R, Bulmer AC, Hörmann-Wallner M, Mölzer C. Oxidative Stress and Related Biomarkers in Gilbert's Syndrome: A Secondary Analysis of Two Case-Control Studies. Antioxidants (Basel). 2021 Sep 15;10(9):1474. https://doi.org/10.3390/antiox10091474
18. ^Matoba N, Une M, Hoshita T. Identification of unconjugated bile acids in human bile. J Lipid Res. 1986 Nov;27(11):1154-62. https://doi.org/10.1016/S0022-2275(20)38751-4

19. ^ *Li XJ, Fang C, Zhao RH, Zou L, Miao H, Zhao YY. Bile acid metabolism in health and ageing-related disease s. Biochem Pharmacol. 2024 Jul;225:116313. https://doi.org/10.1016/j.bcp.2024.116313*

20. ^ *Oxenkrug G, Navrotska V. Extension of life span by down-regulation of enzymes catalyzing tryptophan co nversion into kynurenine: Possible implications for mechanisms of aging. Exp Biol Med (Maywood). 2023 A pr;248(7):573-577. https://doi.org/10.1177/15353702231179411*

21. ^ *Gribble FM, Reimann F. Metabolic Messengers: glucagon-like peptide 1. Nat Metab. 2021;3:142–148. https:// doi.org/10.1038/s42255-020-00327-x*

22. ^ *Chaudhary P, Kathuria D, Suri S, Bahndral A, Kanthi Naveen A. Probiotics- its functions and influence on t he ageing process: A comprehensive review. Food Bioscience. 2023;52:102389. https://doi.org/10.1016/j.fbio.2 023.102389*

23. ^ *Mahboobi S, Ghasvarian M, Ghaem H, Alipour H, Alipour S, Eftekhari MH. Effects of probiotic and magnes ium co-supplementation on mood, cognition, intestinal barrier function and inflammation in individuals w ith obesity and depressed mood: A randomized, double-blind placebo-controlled clinical trial. Front Nutr. 2 022 Sep 28;9:1018357. https://doi.org/10.3389/fnut.2022.1018357*

24. ^ *Seefeldt JM, Homilius C, Hansen J, Lassen TR, Jespersen NR, Jensen RV, et al. Short-Chain Fatty Acid Butyra te Is an Inotropic Agent With Vasorelaxant and Cardioprotective Properties. Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease. 2024;13:109420. https://doi.org/10.1161/JAHA.123.0 33744*

25. ^ *Yu Z, Han J, Chen H, Wang Y, Zhou L, Wang M, et al. Oral Supplementation With Butyrate Improves Myocar dial Ischemia/Reperfusion Injury via a Gut-Brain Neural Circuit. Front Cardiovasc Med. 2021 Sep 23;8:71867 4. https://doi.org/10.3389/fcvm.2021.718674*

26. ^ *Su S, Li X, Yang X, Li Y, Chen X, Sun S, Jia S. Histone acetylation/deacetylation in Candida albicans and thei r potential as antifungal targets. Future Microbiol. 2020 Jul;15:1075-1090. https://doi.org/10.2217/fmb-2019- 0343*

27. ^ *Alseksek RK, Ramadan WS, Saleh E, El-Awady R. The Role of HDACs in the Response of Cancer Cells to Cell ular Stress and the Potential for Therapeutic Intervention. Int J Mol Sci. 2022 Jul 24;23(15):8141. https://doi.or g/10.3390/ijms23158141*

28. ^ *Yu R, Cao X, Sun L, et al. Inactivating histone deacetylase HDA promotes longevity by mobilizing trehalose metabolism. Nat Commun. 2021;12:1981. https://doi.org/10.1038/s41467-021-22257-2*

29. ^ *Silva YP, Bernardi A, Frozza RL. The Role of Short-Chain Fatty Acids From Gut Microbiota in Gut-Brain Co mmunication. Front Endocrinol (Lausanne). 2020 Jan 31;11:25. https://doi.org/10.3389/fendo.2020.00025*

30. ^Sasaki H, Hayashi K, Imamura M, Hirota Y, Hosoki H, Nitta L, et al. Combined resistant dextrin and low-dose Mg oxide administration increases short-chain fatty acid and lactic acid production by gut microbiota. J Nutr Biochem. 2023 Oct;120:109420. https://doi.org/10.1016/j.jnutbio.2023.109420

31. ^Nogal A, Valdes AM, Menni C. "The role of short-chain fatty acids in the interplay between gut microbiota and diet in cardio-metabolic health." Gut Microbes. 2021 Jan-Dec; 13(1):1-24. doi:10.1080/19490976.2021.1897212.

32. ^Menni C, Zierer J, Pallister T, et al. "Omega-3 fatty acids correlate with gut microbiome diversity and production of N-carbamylglutamate in middle aged and elderly women." Scientific Reports. 2017; 7:11079. doi:10.1038/s41598-017-10382-2.

33. ^Fantini C, Corinaldesi C, Lenzi A, Migliaccio S, Crescioli C. "Vitamin D as a Shield against Aging." International Journal of Molecular Sciences. 2023 Feb 25; 24(5):4546. doi:10.3390/ijms24054546.

34. ^Rude RK, Adams JS, Ryzen E, Endres DB, Niimi H, Horst RL, Haddad JG Jr, Singer FR. "Low serum concentrations of 1,25-dihydroxyvitamin D in human magnesium deficiency." The Journal of Clinical Endocrinology & Metabolism. 1985 Nov; 61(5):933-40. doi:10.1210/jcem-61-5-933.

35. ^Ong LTC, Booth DR, Parnell GP. "Vitamin D and its Effects on DNA Methylation in Development, Aging, and Disease." Molecular Nutrition & Food Research. 2020 Dec; 64(23):e2000437. doi:10.1002/mnfr.202000437.

36. ^Daniel T Dibaba. "Effect of vitamin D supplementation on serum lipid profiles: a systematic review and meta-analysis." Nutrition Reviews. 2019 Dec; 77(12):890–902. doi:10.1093/nutrit/nuz037.

37. ^Thomas RL, Jiang L, Adams JS, et al. "Vitamin D metabolites and the gut microbiome in older men." Nature Communications. 2020; 11:5997. doi:10.1038/s41467-020-19793-8.

38. a, bKherad Z, Yazdanpanah S, Saadat F, Pakshir K, Zomorodian K. Vitamin D3: A promising antifungal and antibiofilm agent against Candida species. Curr Med Mycol. 2023 Jun;9(2):17-22. https://pubmed.ncbi.nlm.nih.gov/38375518/

39. ^DeBoy EA, Tassia MG, Schratz KE, Yan SM, Cosner ZL, McNally EJ, Gable DL, Xiang Z, Lombard DB, Antonarakis ES, Gocke CD, McCoy RC, Armanios M. "Familial Clonal Hematopoiesis in a Long Telomere Syndrome." New England Journal of Medicine. 2023 Jun 29; 388(26):2422-2433. doi:10.1056/NEJMoa2300503.

40. ^Ye Q, Apsley AT, Etzel L, Hastings WJ, Kozlosky JT, Walker C, et al. "Telomere length and chronological age across the human lifespan: A systematic review and meta-analysis of 414 study samples including 743,019 individuals." Ageing Research Reviews. 2023 Sep; 90:102031. doi:10.1016/j.arr.2023.102031.

41. ^Maguire D, Neytchev O, Talwar D, McMillan D, Shiels PG. "Telomere Homeostasis: Interplay with Magnesium." International Journal of Molecular Sciences. 2018 Jan 5; 19(1):157. doi:10.3390/ijms19010157.

42. ^ Richards JB, Valdes AM, Gardner JP, Paximadas D, Kimura M, Nessa A, et al, Swaminathan R, Spector TD, A viv A. "Higher serum vitamin D concentrations are associated with longer leukocyte telomere length in wo men." The American Journal of Clinical Nutrition. 2007 Nov; 86(5):1420-5. doi:10.1093/ajcn/86.5.1420.

43. ^ Hu L, Bai Y, Hu G, Zhang Y, Han X, Li J. "Association of Dietary Magnesium Intake With Leukocyte Telomer e Length in United States Middle-Aged and Elderly Adults." Frontiers in Nutrition. 2022 May 19; 9:840804. doi:10.3389/fnut.2022.840804.

44. ^ Hastings WJ, Ye Q, Wolf SE, Ryan CP, Das SK, Huffman KM, Kobor MS, Kraus WE, MacIsaac JL, Martin CK, R acette SB, Redman LM, Belsky DW, Shalev I. "Effect of long-term caloric restriction on telomere length in he althy adults: CALERIE™ 2 trial analysis." Aging Cell. 2024 Jun; 23(6):e14149. doi:10.1111/acel.14149.

45. ^ Ridout KK, Syed SA, Kao HT, Porton B, Rozenboym AV, Tang J, et al. "Relationships Between Telomere Leng th, Plasma Glucagon-like Peptide 1, and Insulin in Early-Life Stress-Exposed Nonhuman Primates." Biologic al Psychiatry Global Open Science. 2021 Aug 3; 2(1):54-60. doi:10.1016/j.bpsgos.2021.07.006.

46. ^ Wang J, Dong X, Cao L, Sun Y, Qiu Y, Zhang Y, Cao R, Covasa M, Zhong L. "Association between telomere len gth and diabetes mellitus: A meta-analysis." Journal of International Medical Research. 2016 Dec; 44(6):115 6-1173. doi:10.1177/0300060516667132.

47. ^ Tosevska A, Moelzer C, Wallner M, Janosec M, Schwarz U, Kern C, et al. "Longer telomeres in chronic, mode rate, unconjugated hyperbilirubinaemia: insights from a human study on Gilbert's Syndrome." Scientific Re ports. 2016 Mar 1; 6:22300. doi:10.1038/srep22300.

48. ^ Dogan F, Forsyth NR. "Telomerase Regulation: A Role for Epigenetics." Cancers. 2021 Mar 10; 13(6):1213. do i:10.3390/cancers13061213.

49. a, b Ojo ES, Tischkau SA. "The Role of AhR in the Hallmarks of Brain Aging: Friend and Foe." Cells. 2021 Oct 1 3; 10(10):2729. doi:10.3390/cells10102729.

50. ^ Wang Z, Snyder M, Kenison JE, Yang K, Lara B, Lydell E, et al. "How the AhR Became Important in Cancer: The Role of Chronically Active AhR in Cancer Aggression." International Journal of Molecular Sciences. 202 0 Dec 31; 22(1):387. doi:10.3390/ijms22010387.

51. ^ Zhu K, Meng Q, Zhang Z, Yi T, He Y, Zheng J, Lei W. "Aryl hydrocarbon receptor pathway: Role, regulation a nd intervention in atherosclerosis therapy (Review)." Molecular Medicine Reports. 2019 Dec; 20(6):4763-477 3. doi:10.3892/mmr.2019.10748.

52. ^ Seo SK, Kwon B. "Immune regulation through tryptophan metabolism." Experimental & Molecular Medici ne. 2023; 55(7):1371–1379. doi:10.1038/s12276-023-01028-7.

53. ^Marinelli L, Martin-Gallausiaux C, Bourhis JM, et al. "Identification of the novel role of butyrate as AhR lig and in human intestinal epithelial cells." Scientific Reports. 2019; 9:643. doi:10.1038/s41598-018-37019-2.

54. a, bLi X, Zhang B, Hu Y, Zhao Y. "New Insights Into Gut-Bacteria-Derived Indole and Its Derivatives in Intesti nal and Liver Diseases." Frontiers in Pharmacology. 2021 Dec 13; 12:769501. doi:10.3389/fphar.2021.769501.

55. ^Rahilly-Tierney C, Sesso HD, Michael Gaziano J, Djoussé L. "High-density lipoprotein and mortality before age 90 in male physicians." Circulation: Cardiovascular Quality and Outcomes. 2012 May; 5(3):381-6. doi:10. 1161/CIRCOUTCOMES.111.963850.

56. ^Franczyk B, Rysz J, Ławiński J, Rysz-Górzyńska M, Gluba-Brzózka A. "Is a High HDL-Cholesterol Level Alw ays Beneficial?" Biomedicines. 2021; 9(9):1083. doi:10.3390/biomedicines9091083.

57. ^Feng M, Darabi M, Tubeuf E, Canicio A, Lhomme M, Frisdal E, et al. "Free cholesterol transfer to high-densi ty lipoprotein (HDL) upon triglyceride lipolysis underlies the U-shape relationship between HDL-cholestero l and cardiovascular disease." European Journal of Preventive Cardiology. 2020 Oct; 27(15):1606-1616. doi:1 0.1177/2047487319894114.

58. ^Basu D, Goldberg IJ. "Regulation of lipoprotein lipase-mediated lipolysis of triglycerides." Current Opinion in Lipidology. 2020 Jun; 31(3):154-160. doi:10.1097/MOL.0000000000000676 and also regulates HDL-C.

59. ^Mathew AA, Panonnummal R. "'Magnesium'-the master cation-as a drug-possibilities and evidences." Bi oMetals. 2021 Oct; 34(5):955-986. doi:10.1007/s10534-021-00328-7.

60. ^Balikai FA, Javali SB, Shindhe VM, Deshpande N, Benni JM, Shetty DP, et al. "Correlation of serum HDL leve l with HRV indices using multiple linear regression analysis in patients with type 2 diabetes mellitus." Diab etes Research and Clinical Practice. 2022 Aug; 190:109988. doi:10.1016/j.diabres.2022.109988.

61. ^Lin SH, Lee IH, Tsai HC, Chi MH, Chang WH, Chen PS, Chen KC, Yang YK. The association between plasma cholesterol and the effect of tryptophan depletion on heart rate variability. The Kaohsiung Journal of Medic al Sciences. 2019;35:440-445. doi:10.1002/kjm2.12067.

62. ^Hernández-Vicente A, Hernando D, Santos-Lozano A, Rodríguez-Romo G, Vicente-Rodríguez G, Pueyo E, et al. Heart Rate Variability and Exceptional Longevity. Frontiers in Physiology. 2020;11:566399. doi:10.3389/fp hys.2020.566399.

63. ^Jarczok MN, Weimer K, Braun C, Williams DP, Thayer JF, Gündel HO, Balint EM. Heart rate variability in th e prediction of mortality: A systematic review and meta-analysis of healthy and patient populations. Neuro science & Biobehavioral Reviews. 2022;143:104907. doi:10.1016/j.neubiorev.2022.104907.

64. ^Gidron Y, Deschepper R, De Couck M, Thayer JF, Velkeniers B. The Vagus Nerve Can Predict and Possibly M odulate Non-Communicable Chronic Diseases: Introducing a Neuroimmunological Paradigm to Public Hea

lth. Journal of Clinical Medicine. 2018;7(10):371. doi:10.3390/jcm7100371.

65. ^*Goswami C, Iwasaki Y, Yada T. Short-chain fatty acids suppress food intake by activating vagal afferent ne urons. The Journal of Nutritional Biochemistry. 2018;57:130-135. doi:10.1016/j.jnutbio.2018.03.009.*

66. ^*Nicoll R, Henein MY. Caloric Restriction and Its Effect on Blood Pressure, Heart Rate Variability and Arteria l Stiffness and Dilatation: A Review of the Evidence. International Journal of Molecular Sciences. 2018;19(3): 751. doi:10.3390/ijms19030751.*

67. ^*Tsubokawa M, Nishimura M, Mikami T, Ishida M, Hisada T, Tamada Y. Association of Gut Microbial Gener a with Heart Rate Variability in the General Japanese Population: The Iwaki Cross-Sectional Research Stud y. Metabolites. 2022;12(8):730. doi:10.3390/metabo12080730.*

68. ^*Kim YH, Jung KI, Song CH. Effects of serum calcium and magnesium on heart rate variability in adult wo men. Biological Trace Element Research. 2012;150(1-3):116-122. doi:10.1007/s12011-012-9518-2.*

69. ^*Lopresti AL. Association between Micronutrients and Heart Rate Variability: A Review of Human Studies. Advances in Nutrition. 2020;11(3):559-575. doi:10.1093/advances/nmz136.*

70. ^*Martín Giménez VM, de Las Heras N, Lahera V, Tresguerres JAF, Reiter RJ, Manucha W. Melatonin as an An ti-Aging Therapy for Age-Related Cardiovascular and Neurodegenerative Diseases. Frontiers in Aging Neur oscience. 2022;14:888292. doi:10.3389/fnagi.2022.888292.*

71. ^*Meng X, Zhou J, Zhao CN, Gan RY, Li HB. Health Benefits and Molecular Mechanisms of Resveratrol: A Nar rative Review. Foods. 2020;9(3):340. doi:10.3390/foods9030340.*

72. ^*Abudahab S, Price ET, Dozmorov MG, Deshpande LS, McClay JL. The Aryl Hydrocarbon Receptor, Epigenet ics and the Aging Process. The Journal of Nutrition, Health and Aging. 2023;27(4):291-300. doi:10.1007/s1260 3-023-1908-1.*

73. ^*Roa FJ, Peña E, Gatica M, Escobar-Acuña K, Saavedra P, Maldonado M, Cuevas ME, Moraga-Cid G, Rivas C I, Muñoz-Montesino C. Therapeutic Use of Vitamin C in Cancer: Physiological Considerations. Frontiers in P harmacology. 2020;11:211. doi:10.3389/fphar.2020.00211.*

74. ^*Cho S, Chae JS, Shin H, Shin Y, Kim Y, Kil EJ, Byun HS, Cho SH, Park S, Lee S, Yeom CH. Enhanced Anticancer Effect of Adding Magnesium to Vitamin C Therapy: Inhibition of Hormetic Response by SVCT-2 Activation. Translational Oncology. 2020;13(2):401-409. doi:10.1016/j.tranon.2019.10.017.*

75. ^*Dang H, Castro-Portuguez R, Espejo L, et al. On the benefits of the tryptophan metabolite 3-hydroxyanthr anilic acid in Caenorhabditis elegans and mouse aging. Nature Communications. 2023;14:8338. doi:10.1038/ s41467-023-43527-1.*

76. ^a, ^b, ^cBozza S, Fallarino F, Pitzurra L, Zelante T, Montagnoli C, Bellocchio S, et al. A Crucial Role for Tryptoph an Catabolism at the Host/Candida albicans Interface. The Journal of Immunology. 2005;174(5):2910-2918. doi:10.4049/jimmunol.174.5.2910.

77. ^Chambers PW. Hyphae and Healthspan: Hypothesis. ResearchGate. 2024. doi:10.13140/RG.2.2.27386.91848.

78. ^a, ^bXue C, Li G, Zheng Q, Gu X, Shi Q, Su Y, et al. Tryptophan metabolism in health and disease. Cell Metaboli sm. 2023;35(8):1304-1326. doi:10.1016/j.cmet.2023.06.004.

79. ^Naeini SH, Mavaddatiyan L, Kalkhoran ZR, Taherkhani S, Talkhabi M. Alpha-ketoglutarate as a potent re gulator for lifespan and healthspan: Evidences and perspectives. Experimental Gerontology. 2023;175:11215 4. doi:10.1016/j.exger.2023.112154.

80. ^Abraham KJ, Chan JN, Salvi JS, Ho B, Hall A, Vidya E, Guo R, Killackey SA, Liu N, Lee JE, Brown GW, Mekhail K. Intersection of calorie restriction and magnesium in the suppression of genome-destabilizing RNA-DNA hybrids. Nucleic Acids Research. 2016;44(18):8870-8884. doi:10.1093/nar/gkw752.

81. ^Cox MF, Hascup ER, Bartke A, Hascup KN. Friend or Foe? Defining the Role of Glutamate in Aging and Alzh eimer's Disease. Frontiers in Aging. 2022;3:929474. doi:10.3389/fragi.2022.929474.

82. ^a, ^b, ^cZhang Y, Jelleschitz J, Grune T, Chen W, Zhao Y, Jia M, et al. Methionine restriction - Association with re dox homeostasis and implications on aging and diseases. Redox Biology. 2022;57:102464. doi:10.1016/j.redo x.2022.102464.

83. ^Liu Y, Guo J, Cheng H, Wang J, Tan Y, Zhang J, et al. Methionine Restriction Diets: Unravelling Biological Me chanisms and Enhancing Brain Health. Trends in Food Science & Technology. 2024;149:104532. doi:10.1016/ j.tifs.2024.104532.

84. ^Mukherjee S, Banerjee O, Singh S. The Role of B Vitamins in Protecting Mitochondrial Function. Chapter 6, Molecular Nutrition and Mitochondria. 2023;167-193. doi:10.1016/B978-0-323-90256-4.00001-1.

85. ^Long DM, Frame AK, Reardon PN, Cumming RC, Hendrix DA, Kretzschmar D, et al. Lactate dehydrogenase expression modulates longevity and neurodegeneration in Drosophila melanogaster. Aging. 2020;12(11):100 41-10058. doi:10.18632/aging.103373.

86. ^Zhou Y, Qi M, Yang M. Current Status and Future Perspectives of Lactate Dehydrogenase Detection and Me dical Implications: A Review. Biosensors. 2022;12(12):1145. doi:10.3390/bios12121145.

87. ^Louis P, Duncan SH, Sheridan PO, Walker AW, Flint HJ. Microbial lactate utilisation and the stability of the gut microbiome. Gut Microbiome. 2022;3:e3. doi:10.1017/gmb.2022.3.

88. ^Singh V, Lee G, Son H, Koh H, Kim ES, Unno T, et al. Butyrate producers, "The Sentinel of Gut": Their intesti nal significance with and beyond butyrate, and prospective use as microbial therapeutics. Frontiers in Micr

obiology. 2023;13:1103836. doi:10.3389/fmicb.2022.1103836.

89. ^*Lee M-C, Hsu Y-J, Ho H-H, Hsieh S-H, Kuo Y-W, Sung H-C, et al. Lactobacillus salivarius Subspecies saliciniu s SA-03 is a New Probiotic Capable of Enhancing Exercise Performance and Decreasing Fatigue. Microorga nisms. 2020;8(4):545. doi:10.3390/microorganisms8040545.*

90. ^*Gupta GS. The Lactate and the Lactate Dehydrogenase in Inflammatory Diseases and Major Risk Factors i n COVID-19 Patients. Inflammation. 2022;45(6):2091-2123. doi:10.1007/s10753-022-01680-7.*

91. ^*Seale K, Horvath S, Teschendorff A, Eynon N, Voisin S. "Making sense of the ageing methylome". Nat Rev G enet. 23 (10): 585–605. doi:10.1038/s41576-022-00477-6.*

92. ^*Salameh Y, Bejaoui Y, El Hajj N. "DNA Methylation Biomarkers in Aging and Age-Related Diseases". Front Genet. 2020 Mar 10; 11: 171. doi:10.3389/fgene.2020.00171.*

93. ^*Horvath S, Raj K. "DNA methylation-based biomarkers and the epigenetic clock theory of ageing". Nat Rev Genet. 19 (6): 371–384. doi:10.1038/s41576-018-0004-3.*

94. ^*Milicic L, Porter T, Vacher M, Laws SM. "Utility of DNA Methylation as a Biomarker in Aging and Alzheime r's Disease". J Alzheimers Dis Rep. 2023 May 31; 7 (1): 475–503. doi:10.3233/ADR-220109.*

95. ^*MTHFR Gene Variant and Folic Acid Facts https://www.cdc.gov/folic-acid/data-research/mthfr/index.html*

96. ^*Moll S, Varga E. "Homocysteine and MTHFR Mutations". Circulation. 132 (1). doi:10.1161/CIRCULATIONAH A.114.013311.*

97. ^*Barbagallo M, Veronese N, Dominguez LJ. "Magnesium in Aging, Health and Diseases". Nutrients. 13 (2): 46 3. doi:10.3390/nu13020463.*

98. ^*Khaidizar FD, Bessho Y, Nakahata Y. "Nicotinamide Phosphoribosyltransferase as a Key Molecule of the A ging/Senescence Process". Int J Mol Sci. 2021 Apr 2; 22 (7): 3709. doi:10.3390/ijms22073709.*

99. ^*Castro-Portuguez R, Sutphin GL. "Kynurenine pathway, NAD+ synthesis, and mitochondrial function: Tar geting tryptophan metabolism to promote longevity and healthspan". Exp Gerontol. 2020 Apr; 132: 110841. doi:10.1016/j.exger.2020.110841.*

100. ^*Zhang C, Zhang T, Zou J, Miller CL, Gorkhali R, Yang JY, et al. "Structural basis for regulation of human calc ium-sensing receptor by magnesium ions and an unexpected tryptophan derivative co-agonist". Sci Adv. 20 16 May 27; 2 (5): e1600241. doi:10.1126/sciadv.1600241.*

101. ^*Ferrè S, Hoenderop JG, Bindels RJ. "Sensing mechanisms involved in Ca2+ and Mg2+ homeostasis". Kidney Int. 2012 Dec; 82 (11): 1157–1166. doi:10.1038/ki.2012.179.*

102. ^a, ^b*Essex M, Millet Pascual-Leone B, Löber U, et al. "Gut microbiota dysbiosis is associated with altered trypt ophan metabolism and dysregulated inflammatory response in COVID-19". npj Biofilms Microbiomes. 10*

(1): 66. doi:10.1038/s41522-024-00538-0.

103. ^*Bidell MR, Hobbs ALV, Lodise TP. "Gut microbiome health and dysbiosis: A clinical primer". Pharmacother apy. 2022 Nov; 42 (11): 849–857. doi:10.1002/phar.2731.*

104. a, b*Salazar J, Durán P, Díaz MP, Chacín M, Santeliz R, Mengual E, et al. "Exploring the Relationship between the Gut Microbiota and Ageing: A Possible Age Modulator". Int J Environ Res Public Health. 2023 May 17; 20 (10): 5845. doi:10.3390/ijerph20105845.*

105. ^*Cerqueira NM, Brás NF, Ramos MJ, Fernandes PA. "Glycosidases – A Mechanistic Overview". https://doi.or g/10.5772/52019*

106. ^*Ferenc K, Sokal-Dembowska A, Helma K, Motyka E, Jarmakiewicz-Czaja S, Filip R. "Modulation of the Gut Microbiota by Nutrition and Its Relationship to Epigenetics". Int J Mol Sci. 2024 Jan 19; 25 (2): 1228. doi:10.33 90/ijms25021228.*

107. ^*Schiopu C, Ștefănescu G, Diaconescu S, Bălan GG, Gimiga N, Rusu E, et al. "Magnesium Orotate and the Mic robiome-Gut-Brain Axis Modulation: New Approaches in Psychological Comorbidities of Gastrointestinal F unctional Disorders". Nutrients. 2022 Apr 9; 14 (8): 1567. doi:10.3390/nu14081567.*

108. ^*Hardwick LL, Jones MR, Brautbar N, Lee DB. "Magnesium absorption: mechanisms and the influence of vit amin D, calcium and phosphate". J Nutr. 1991 Jan; 121 (1): 13–23. doi:10.1093/jn/121.1.13.*

109. a, b*Rosanoff A, Dai Q, Shapses SA. "Essential Nutrient Interactions: Does Low or Suboptimal Magnesium Sta tus Interact with Vitamin D and/or Calcium Status?". Adv Nutr. 2016 Jan; 7 (1): 25–43. doi:10.3945/an.115.008 631.*

110. ^*Ashique S, Kumar S, Hussain A, Mishra N, Garg A, Gowda BHJ, et al. "A narrative review on the role of mag nesium in immune regulation, inflammation, infectious diseases, and cancer". J Health Popul Nutr. 2023 Jul 27; 42 (1): 74. doi:10.1186/s41043-023-00423-0.*

111. ^*Yang Z, Zhang Y, Gao J, Yang Q, Qu H, Shi J. "Association between dietary magnesium and 10-year risk of a first hard atherosclerotic cardiovascular disease event". Am J Med Sci. 2024 May 26; 368 (4): 355–360. doi:1 0.1016/j.amjms.2024.05.014.*

112. ^*Du K, Zheng X, Ma ZT, Lv JY, Jiang WJ, Liu MY. "Association of Circulating Magnesium Levels in Patients Wi th Alzheimer's Disease From 1991 to 2021: A Systematic Review and Meta-Analysis". Front Aging Neurosci. 2 022 Jan 10; 13: 799824. doi:10.3389/fnagi.2021.799824.*

113. ^*Deng X, Song Y, Manson JE, et al. "Magnesium, vitamin D status and mortality: results from US National H ealth and Nutrition Examination Survey (NHANES) 2001 to 2006 and NHANES III". BMC Med. 11 (1): 187. d oi:10.1186/1741-7015-11-187.*

114. ^Costello RB, Elin RJ, Rosanoff A, Wallace TC, Guerrero-Romero F, Hruby A, Lutsey PL, Nielsen FH, Rodrigue z-Moran M, Song Y, et al. "Perspective: The Case for an Evidence-Based Reference Interval for Serum Magn esium: The Time Has Come". Adv Nutr. 2016; 7: 977–993. doi:10.3945/an.116.012765.

115. ^Razzaque MS. "Magnesium: Are We Consuming Enough?". Nutrients. 10 (12): 1863. doi:10.3390/nu10121863.

116. ^Elin RJ. Assessment of magnesium status for diagnosis and therapy. Magnes Res. 2010 Dec;23(4):S194-8. ht tps://doi.org/10.1684/mrh.2010.0213

117. ^Micke O, Vormann J, Kraus A, Kisters K. "Serum Magnesium: Time for a Standardized and Evidence-Based Reference Range". Magnetic Resonance, 34, 84-89. https://www.magnesium-ges.de/Micke_et_al._2021.pdf

118. ^Rosanoff A, West C, Elin RJ, Micke O, Baniasadi S, Barbagallo M, et al. "MaGNet Global Magnesium Project (MaGNet). Recommendation on an updated standardization of serum magnesium reference ranges". Eur J Nutr. 2022 Oct; 61 (7): 3697–3706. doi:10.1007/s00394-022-02916-w.

119. ^Weiss D, Brunk DK, Goodman DA. "Scottsdale Magnesium Study: Absorption, Cellular Uptake, and Clinical Effectiveness of a Timed-Release Magnesium Supplement in a Standard Adult Clinical Population". J Am Co ll Nutr. 2018 May-Jun; 37 (4): 316–327. doi:10.1080/07315724.2017.1398686.

120. ^Hoy MK, Goldman JD. Calcium intake of the U.S. population: What We Eat in America, NHANES 2009-201 0. 2014 Sep. https://www.ncbi.nlm.nih.gov/books/NBK589560/

121. ^Shlisky J, Mandlik R, Askari S, Abrams S, Belizan JM, Bourassa MW, Cormick G, Driller-Colangelo A, Gomes F, Khadilkar A, Owino V, Pettifor JM, Rana ZH, Roth DE, Weaver C. Calcium deficiency worldwide: prevalenc e of inadequate intakes and associated health outcomes. Ann N Y Acad Sci. 2022 Jun;1512(1):10-28. doi:10.111 1/nyas.14758.

122. ^Guerrero-Romero F, Mercado M, Rodriguez-Moran M, et al. Magnesium-to-Calcium Ratio and Mortality f rom COVID-19. Nutrients. 2022 Apr;14(9):1686. doi:10.3390/nu14091686.

123. ^La Carrubba A, Veronese N, Di Bella G, Cusumano C, Di Prazza A, Ciriminna S, et al. Prognostic Value of M agnesium in COVID-19: Findings from the COMEPA Study. Nutrients. 2023 Feb 6;15(4):830. doi:10.3390/nu15 040830.

124. ^Fan L, Zhu X, Zheng Y, Zhang W, Seidner DL, Ness R, Murff HJ, Yu C, Huang X, Shrubsole MJ, Hou L, Dai Q. M agnesium treatment on methylation changes of transmembrane serine protease 2 (TMPRSS2). Nutrition. 2 021 Sep;89:111340. doi:10.1016/j.nut.2021.111340.

125. ^Balnis J, Madrid A, Drake LA, Vancavage R, Tiwari A, Patel VJ, et al. Blood DNA methylation in post-acute s equelae of COVID-19 (PASC): a prospective cohort study. EBioMedicine. 2024 Aug;106:105251. doi:10.1016/j.eb iom.2024.105251.

126. ^Ponti G, Pastorino L, Manfredini M, Ozben T, Oliva G, Kaleci S, Iannella R, Tomasi A. COVID-19 spreading a cross world correlates with C677T allele of the smethylenetetrahydrofolate reductase (MTHFR) gene preval ence. J Clin Lab Anal. 2021 Jul;35(7):e23798. doi:10.1002/jcla.23798.

127. a, bAbraham, G.E.; Schwartz, U.D.; Lubran, M.M. Effect of vitamin B-6 on plasma and red blood cell magnesi um levels in premenopausal women. Ann. Clin. Lab. Sci. 1981, 11, 333–336 https://pubmed.ncbi.nlm.nih.gov/7 271227/.

128. a, bBoylan, L.M.; Spallholz, J.E. In vitro evidence for a relationship between magnesium and vitamin B-6. M agnes. Res. 1990, 3, 79–85 https://pubmed.ncbi.nlm.nih.gov/2133627/.

129. ^Noah, L., Pickering, G., Dubray, C., Mazur, A., Hitier, S., & Pouteau, E. (2020). Effect of vitamin B6 supplemen tation, in combination with magnesium, on severe stress and magnesium status: Secondary analysis from a n RCT. Proceedings of the Nutrition Society, 79(OCE2), E491. doi:10.1017/S0029665120004395.

130. ^Pouteau E, Kabir-Ahmadi M, Noah L, Mazur A, Dye L, Hellhammer J, Pickering G, Dubray C. Superiority of magnesium and vitamin B6 over magnesium alone on severe stress in healthy adults with low magnesemi a: A randomized, single-blind clinical trial. PLoS One. 2018 Dec 18;13(12):e0208454. doi:10.1371/journal.pone. 0208454.

131. ^Eisinger J, Dagorn J. Vitamin B6 and magnesium. Magnesium. 1986;5(1):27-32. https://pubmed.ncbi.nlm.ni h.gov/3959594/.

132. ^Planells E, Lerma A, Sánchez-Morito N, Aranda P, LLopis J. Effect of magnesium deficiency on vitamin B2 and B6 status in the rat. J Am Coll Nutr. 1997 Aug;16(4):352-6. doi:10.1080/07315724.1997.10718697.

133. ^Vrolijk MF, Opperhuizen A, Jansen EHJM, Hageman GJ, Bast A, Haenen GRMM. The vitamin B6 paradox: S upplementation with high concentrations of pyridoxine leads to decreased vitamin B6 function. Toxicol In Vitro. 2017 Oct;44:206-212. doi:10.1016/j.tiv.2017.07.009.

134. ^Mikkelsen K, Apostolopoulos V. B Vitamins and Ageing. Subcell Biochem. 2018;90:451-470. doi:10.1007/978 -981-13-2835-0_15.

135. ^Stoff R, Wolf Y, Boursi B. Fecal Microbiota Transplantation as a Cancer Therapeutic. Cancer J. 2023 Mar-Ap r 01;29(2):102-108. doi:10.1097/PPO.0000000000000651.

136. ^Liu X, Liu M, Zhao M, Li P, Gao C, Fan X, Cai G, Lu Q, Chen X. Fecal microbiota transplantation for the mana gement of autoimmune diseases: Potential mechanisms and challenges. J Autoimmun. 2023 Dec;141:103109. doi:10.1016/j.jaut.2023.103109.

137. ^Wang, H., Yang, F., Zhang, S. et al. Genetic and environmental factors in Alzheimer's and Parkinson's diseas es and promising therapeutic intervention via fecal microbiota transplantation. npj Parkinsons Dis. 7, 70 (2

021). doi:10.1038/s41531-021-00213-7.

138. ^*Matsuoka, H. (2005) Aldosterone and Magnesium. Clinical Calcium, 15, 187-191. https://pubmed.ncbi.nlm.nih.gov/15692156/.*

139. ^*Piuri G, Zocchi M, Della Porta M, Ficara V, Manoni M, Zuccotti GV, Pinotti L, Maier JA, Cazzola R. Magnesium in Obesity, Metabolic Syndrome, and Type 2 Diabetes. Nutrients. 2021 Jan 22;13(2):320. doi:10.3390/nu13020320.*

140. ^*Dan J, Yang J, Liu Y, Xiao A, Liu L. Roles for Histone Acetylation in Regulation of Telomere Elongation and Two-cell State in Mouse ES Cells. J Cell Physiol. 2015 Oct;230(10):2337-44. doi:10.1002/jcp.24980.*

141. ^*Jones G, Prosser DE, Kaufmann M. Cytochrome P450-mediated metabolism of vitamin D. J Lipid Res. 2014 Jan;55(1):13-31. doi:10.1194/jlr.R031534.*

142. ^*Chen J, Zhao KN, Chen C. The role of CYP3A4 in the biotransformation of bile acids and therapeutic implication for cholestasis. Ann Transl Med. 2014 Jan;2(1):7. https://doi.org/10.3978/j.issn.2305-5839.2013.03.02.*

143. ^*Pikuleva IA. Cholesterol-metabolizing cytochromes P450: implications for cholesterol lowering. Expert Op in Drug Metab Toxicol. 2008 Nov;4(11):1403-14. doi:10.1517/17425255.4.11.1403.*

144. ^*Li X, Zhang B, Hu Y, Zhao Y. New Insights Into Gut-Bacteria-Derived Indole and Its Derivatives in Intestinal and Liver Diseases. Front Pharmacol. 2021 Dec 13;12:769501. doi:10.3389/fphar.2021.769501.*

145. ^*Pludowski P, Holick MF, Pilz S, et al. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-a review of recent evidence. Autoimmunity Reviews. 2013 Aug;12(10):976-989. doi:10.1016/j.autrev.2013.02.004.*

146. ^*Laborde S, Mosley E, Thayer JF. Heart Rate Variability and Cardiac Vagal Tone in Psychophysiological Research - Recommendations for Experiment Planning, Data Analysis, and Data Reporting. Front Psychol. 2017 Feb 20;8:213. doi:10.3389/fpsyg.2017.00213.*

147. ^*Shanmukha KD, Paluvai H, Lomada SK, Gokara M, Kalangi SK. Histone deacetylase (HDACs) inhibitors: Clinical applications. Prog Mol Biol Transl Sci. 2023;198:119-152. doi:10.1016/bs.pmbts.2023.02.011.*

148. ^*Banik D, Moufarrij S, Villagra A. Immunoepigenetics Combination Therapies: An Overview of the Role of HDACs in Cancer Immunotherapy. International Journal of Molecular Sciences. 2019; 20(9):2241. doi:10.3390/ijms20092241.*

149. ^*Guha, S., Jagadeesan, Y., Pandey, M.M., Mittal, A., & Chitkara, D. (2024). Targeting the epigenome with advanced delivery strategies for epigenetic modulators. Bioengineering & Translational Medicine. doi:10.1002/btm2.10710.*

150. ^ *Zhang S, Kiarasi F. Therapeutic effects of resveratrol on epigenetic mechanisms in age-related diseases: A comprehensive review. Phytother Res. 2024 May;38(5):2347-2360. doi:10.1002/ptr.8176.*

Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.