Review Article

Calcium-Magnesium Balance—Clinical Implications for Global Human Health

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Magnesium is essential for vitamin D_3 metabolism and optimum function, supporting enzymes that synthesize 25(OH) D and calcitriol and facilitating receptor binding. Optimizing the Ca: Mg ratio likely enhances vitamin D efficacy and improves outcomes. Beyond this, Mg is vital for G-protein-coupled receptor function, CYP450 enzyme activity, activation of B vitamins, epigenetic methylation, glucose metabolism, and mitigating oxidative stress and inflammaging. Assessing serum Mg (mmol/L) offers a more physiologically relevant measure than dietary intake (mg/day). Mean ionized Ca and Mg levels yield an iCa: iMg ratio within the optimal range; however, since Mg is distributed in both plasma and red blood cells while Ca is largely extra-cellular, a 3:2 intake ratio may better support homeostasis than the commonly recommended 2:1. Calcium and magnesium function as physiological opposites; their ratio (optimal 1.7-2.6) is a key indicator of health and disease risk. An imbalanced Ca: Mg ratio—outside this range—increases risks for cancer, cardiovascular disease, dementia, infections (including COVID-19 complications), and post-COVID syndrome. Conversely, obesity is both a cause and consequence of Ca: Mg imbalance. Magnesium deficiency likely contributes to the global prevalence of type 2 diabetes, which shares features with aging. Evidence from laboratory reference ranges, NHANES data, and peer-reviewed studies underscores the need for clinical validation of these observations. Globally, magnesium deficiency remains prevalent and understudied in clinical trials. Study data support that maintaining optimal Ca:Mg ratios benefits cancer prevention and common disorders. Optimizing the Ca: Mg ratio is a cost-effective, globally impactful strategy to improve metabolic health and reduce chronic disease risk.

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Highlights

- A balanced Ca: Mg (1.7-2.6) suppresses cancer, heart disease, dementia, infections, and COVID-19.
- A high molecular Ca: Mg and low Mg, often seen in those on a Western diet, herald premature aging.
- Vitamin D deficiency and low molecular Ca, more frequently encountered elsewhere, tend to lower Ca: Mg.
- Mg deficiency compromises PTH-dependent Ca absorption and the synthesis and efficacy of all forms of vitamin D.
- A balanced Ca: Mg enhances the benefits of vitamin D.
- A 3:2 Ca to Mg intake ratio may better support mineral balance than the traditional 2:1.

Introduction

The global decline in health, with widespread micronutrient deficiencies playing a central role, is a growing topic. Among the most overlooked are molecualr calcium (Ca) and magnesium (Mg)—the body's most abundant cations after sodium and potassium. Although deficiencies in both minerals are well documented, the benefits of supplementing one in isolation remain unclear. Researchers now view the Ca: Mg ratio as more pertinent than their absolute levels. In 1989, Durlach proposed an ideal intake ratio of 2:1 by weight [1][2], but the optimal method for measuring and calculating this ratio—whether through dietary intake or blood levels—remains debated. This mini review introduces a novel approach using laboratory reference ranges from healthy populations, comparing total serum Ca and Mg (mmol/L), ionized Ca and Mg, and RBC Mg to define optimal physiological balance.

Physiological Roles Cell Signaling to Cell Death: Calcium (Ca) and Magnesium (Mg)

Ca^{2+} and Mg^{2+} are essential divalent cations that play critical—and often opposing—roles in cellular physiology, ranging from signal transduction to apoptosis. Intracellular Ca is a ubiquitous second messenger, regulating numerous processes, including muscle contraction, neurotransmitter release, gene expression, enzyme activation, and programmed cell death [3]. In contrast, Mg acts as a natural Ca antagonist, stabilizing ATP, modulating ion channels, and maintaining membrane potential and genomic integrity [4].

While transient intracellular Ca^{2+} spikes initiate essential cellular responses, prolonged elevation can induce oxidative stress and activate both caspase-dependent and -independent apoptotic pathways [5]. By buffering Ca^{2+} influx, Mg^{2+} regulates mitochondrial permeability transition pores and protects against calcium-induced cytotoxicity and cell death. The precise balance between these ions is critical: disruptions in their ratio contribute to a range of pathologies, including cardiovascular diseases, neurodegeneration, and metabolic disorders [6]. Understanding the dynamic interplay between Ca^{2+} and Mg^{2+} offers valuable insights into cellular fate decisions and offers potential avenues for therapeutic intervention.

Importance of maintaining a balanced Ca: Mg ratio for overall health

Magnesium (Mg^{2+}) deficiency and an elevated calcium-to-magnesium (Ca^{2+}: Mg^{2+}) ratio are recognized increasingly as contributors to chronic low-grade inflammation and oxidative stress—key drivers of a process known as inflammaging [7]. Inflammaging, characterized by systemic, age-related inflammation in the absence of infection, is closely linked to the pathogenesis of numerous age-related diseases. Research has shown that low Mg^{2+} levels can trigger the release of pro-inflammatory cytokines and increase oxidative stress markers [8]. These responses accelerate cellular aging and dysfunction, directly associating an elevated Ca^{2+}: Mg^{2+} ratio with conditions such as cardiovascular disease, type 2 diabetes, and neurodegenerative disorders like Alzheimer's disease [9][10].

An imbalanced Ca^{2+}: Mg^{2+} ratio has been directly linked to the onset and progression of cardiovascular risk [11] and mortality [12][13], cancer, autoimmune disorders, infections, dementia [14][15], and obesity [16] [17]. Although both Ca and Mg are essential minerals, their physiological actions are often antagonistic, making their balance vital for homeostasis. Excess Ca intake without sufficient Mg can promote uncontrolled cell proliferation—a hallmark of cancer—while Mg deficiency may impair DNA repair mechanisms and increase oxidative DNA damage [18]. However, the relationship between Ca, Mg, and cancer remains inconsistent [8], partly due to variations in study populations, dietary intake, methodologies, and the lack of consideration for their interactive effects [19]. Thus, studies should evaluate the Ca^{2+}: Mg^{2+} ratio rather than individual mineral levels when assessing disease risk and developing dietary guidelines.

Physiology of Calcium and Magnesium

Calcium is a vital mineral in human physiology, essential for supporting the structural integrity of bones and teeth, supporting neuromuscular signaling, enabling blood coagulation, and facilitating hormone

secretion. It also serves as a key intracellular messenger, regulating various cellular functions, including muscle contraction, neurotransmitter release, and enzyme activity. Intracellular Ca^{2+} levels are controlled tightly by calcium-binding proteins, membrane channels, and organelles such as the endoplasmic reticulum and mitochondria to prevent cytotoxic overload [20]. Extra-cellular Ca concentrations are maintained within a narrow range through hormonal regulation involving parathyroid hormone, calcitonin, and active vitamin D (calcitriol), thereby preserving physiological balance and homeostasis [21].

Magnesium, the second most abundant intracellular cation, is a critical cofactor in over 600 enzymatic reactions, particularly in ATP metabolism, DNA replication, and protein synthesis [22]. It plays a central role in stabilizing nucleic acids, modulating ion channels, and mitigating calcium-mediated excitotoxicity. Mg^{2+} is also essential for cardiovascular, neuromuscular, and immune function while maintaining cellular electrical gradients and mitochondrial integrity [23][24]. Intestinal absorption and renal excretion regulate Mg homeostasis. Mg^{2+} deficiency—often underdiagnosed—can result in neuromuscular disorders, arrhythmias, insulin resistance, and chronic inflammation, highlighting its indispensable physiological functions [25].

Calcium

Ca^{2+} and Mg^{2+} are vital to human physiology. Although there is some functional overlap, these two ions primarily occupy opposite roles and have different counteracting functions. Ca^{2+} is predominantly extra-cellular, with a concentration of four orders of magnitude greater than that within the cell [1]. Nevertheless, Ca^{2+} and Ca/Mg ratio function as a second messenger from the circulation to cells and within cells, particularly those with calcium-sensing receptors (CaSRs), such as parathyroid cells, renal tubular cells, etc. Its primary extra-cellular role is the maintenance of skeletal and dental health. It is also vital for muscle contraction and nerve transmission.

Serum Ca^{2+} is the primary determinant of parathyroid hormone (PTH) secretion and the release of calcitonin in response to calcium stress situations [1]. Additionally, the intrinsic clotting cascade is highly dependent on Ca^{2+}. Although Ca^{2+} is primarily extra-cellular, its intracellular concentration is linked to signaling, inflammaging, and oxidative stress [7]. Half of the circulating plasma calcium is bound to protein, primarily albumin, while the other half exists in the ionized form. Laboratory reports often provide a corrected serum value when blood albumin is low; however, this is unnecessary [26].

Magnesium

Intracellular versus extra-cellular concentration of magnesium varies by cell type but is typically more than three times higher intracellularly. Meanwhile, Mg-dependent ATP maintains the high 1:10,000 gradient for Ca^{2+}. The latter also maintains the 30:1 gradient for intracellular potassium [27] and the 1:50 gradient for extra-cellular sodium [28]. Consequently, it would be challenging to maintain intracellular potassium levels or sustain normocalemia in the face of a Mg shortfall.

Hypermagnesemia: It leads to cardiovascular complications, such as hypotension and bradycardia. In extreme cases, it can cause cardiac arrest due to the inhibitory effect of Mg on Ca-mediated cardiac conduction pathways [29]. Elevated Mg^{2+} levels may lead to depressed central nervous system activity, including respiratory depression or even coma [30]. Consequently, severe hypermagnesemia (>6.0 mg/dL) is a medical emergency that may require interventions, including intravenous Ca gluconate and short-term renal replacement therapy to reduce Mg levels rapidly [31]. The key is recognizing early with prompt interventions to prevent life-threatening clinical outcomes [32].

Hypomagnesemia: Magnesium is essential for many physiological functions, including enzymatic activity, hormone synthesis and release, neuromuscular function, cellular energy balance, and receptor activation [33][34]. Thus, it is unsurprising that it can seriously affect human health. Examples include muscle weakness, cramps, tremors, and fatigue [32]. Magnesium is crucial for maintaining proper heart rhythm and regulating potassium and Ca ions in cardiac tissues; thus, hypomagnesemia can lead to cardiac arrhythmias [35].

Chronic hypomagnesemia contributes to several long-term health problems, such as the increased risk of falls, osteoporosis and fractures [36], insulin resistance, and hypertension. Nevertheless, the circulatory Mg concentrations do not accurately reflect tissue Mg levels [37]. As with higher levels, the lower tissue Mg can lead to cardiac arrhythmia, nerve conduction defects, and muscle weakness [34]. It also impairs parathyroid gland functions, simulates hypoparathyroidism, and exacerbates conditions such as diabetes and metabolic syndrome [35]. In severe cases, it can lead to life-threatening complications, such as respiratory distress and seizures [38]. Early diagnosis and management, through dietary adjustments or supplementation, are crucial to prevent adverse outcomes and restore Mg balance in the body [39][40].

Hypomagnesemia also disrupts hormone synthesis, release, and vitamin D activity (see below) [41]. It is associated with decreased synthesis and activation of vitamin D and VDR interactions, increased oxidative

stress, and exacerbated cytotoxic activity in T lymphocytes, promoting the cytokine storm [42][43]. In addition, hypomagnesemia can cause endothelial dysfunction [44][45] and impaired myocardial contractility, hence increasing the risk of developing heart failure [46]. Those with hypomagnesemia with severe SARS-CoV-2 infection [47][48][49] or following COVID-19 vaccines can experience serious adverse effects [50][51]. The physiological and biological functions of Mg are numerous. The renal outer medullary potassium channel (ROMK) is an Mg-dependent ATP channel that recycles potassium. Mg^{2+} is critical in inhibiting ROMK potassium channels in the principal cells of collecting tubules and ducts. When magnesium levels drop, ROMK channels become hyperactive—another mechanism of hypokalemia in hypomagnesemia.

Magnesium and Healthy Aging

Most enzymes that involve ATP/GTP, ADP/GDP, or cAMP/cGMP require physiological concentrations of Mg^{2+} [33][52]. Mg serves many disparate functions, some of which impact aging:

1. G-protein coupled receptors (GPCRs) are Mg-dependent (GTP), including those for Ca/Mg (CaSR) [53][54], PTH, and insulin secretion [53]. Although VDR (vitamin D receptor) on the nuclear membrane is well known, there is another VDR-like membrane receptor, 1,25-D_3-MARRS (membrane-associated, rapid response steroid-binding), on the cell membrane [55]. It is also a GPCR and potentiates immune function, e.g., breast cancer prevention [56].
2. Mg-dependent cAMP (second messenger) intracellular signaling is also involved in VDR activation. Thirty-four per cent of FDA-approved drugs target GPCRs [55]. Not surprisingly, decreased efficiency of GPCR signaling may mediate age-related disease [53][54][57]. TRH (thyrotropin-releasing hormone) and TSH (thyroid-stimulating hormone) are ligands for Mg-dependent GPCRs. Iodination of T4 to form T3 is Mg-dependent.
3. All CYP450 enzymes require Mg as a cofactor, some of which are involved in synthesizing vitamin D [56][58] (see Figure 1). CYP450 activity declines with age [59].
4. Another CYP450 enzyme, Mg-dependent 11β-hydroxysteroid dehydrogenase, degrades cortisol [60], tightly linked to cognitive decline and dementia [61].

Figure 1 illustrates the crucial role of magnesium in the biochemistry of vitamin D synthesis.

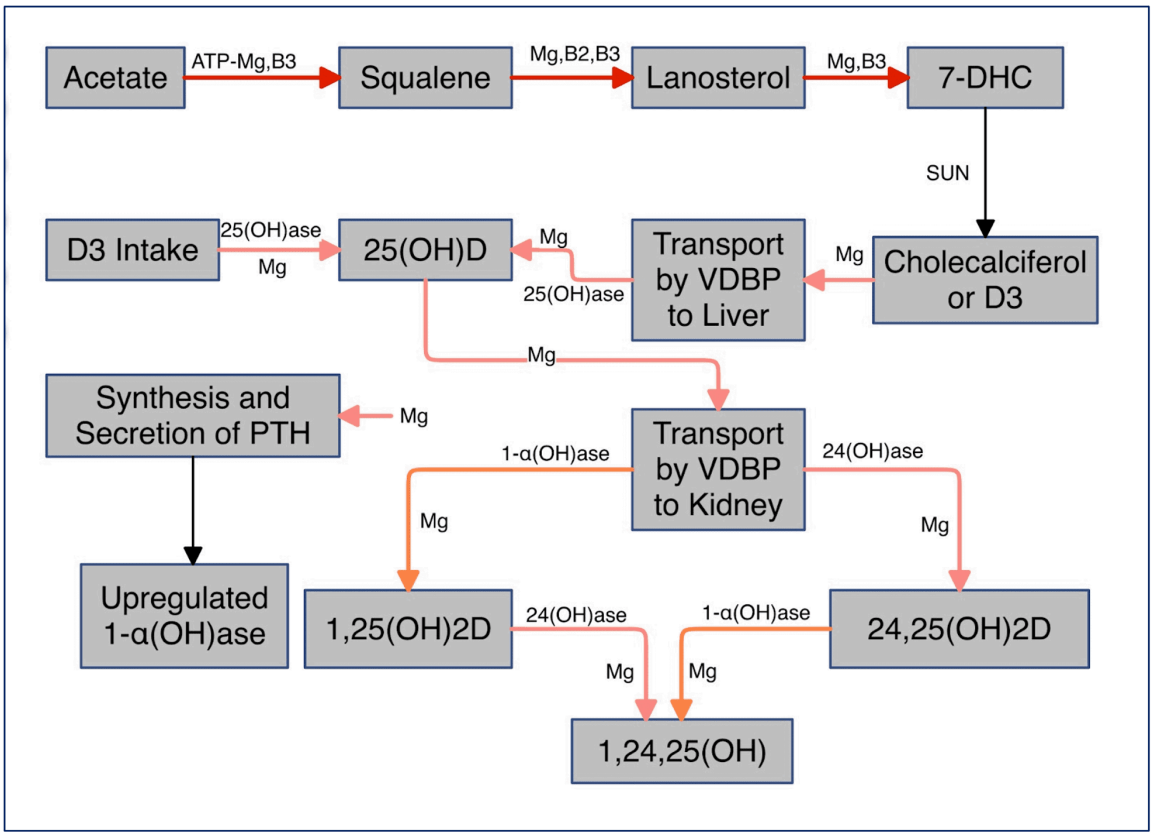

Figure 1. Synthesis of not only 7-dehydrocholesterol [19][62], the substrate for UVB-dependent production of D_3, but also the storage of 25(OH) D and active form $1,25(OH)_2D$, metabolites of vitamin D requires ATP-Mg, cofactor Mg, and Mg-dependent B2 and B3. The figure was created from fundamentals discussed by Han Y., et al., 2025 [62] and Chambers P. (2025) [19].

In addition to optimal GPCR function, CYP450 enzymes, and vitamin D synthesis [53], Mg is a required cofactor for most glycolytic pathway and Krebs cycle enzymes. Many phosphorylation reactions are also Mg-dependent, e.g., activation of vitamins B1 (thiamine to thiamine pyrophosphate) [63], B2 (riboflavin to FAD) [64], B3 (niacin to NAD) [65], B5 (pantothenate to coenzyme A) [66], and B6 (pyridoxine to pyridoxal phosphate) [52]. Methylation reactions are also Mg-dependent, e.g., activation of B9 (folate to methyl folate) and B12 (cyanocobalamin to methylcobalamin) [67], require Mg as a cofactor [33][52]. All but biotin (B7) require Mg-dependent activation, and their deficiencies accelerate aging [68]. DNA methylation protects the genome, and decreased DNA methylation is a hallmark of aging [69]. Differential DNA methylation has recently been reported in cancer [70], dementia [70], cardiovascular disease (CVD) [71], and autoimmune disease [72], including Covid-19 severity and post-COVID syndrome [73].

Magnesium-dependent enzymes account for 80% of known metabolic functions [74]. Figure 1 illustrates the crucial roles of Mg, including synthesizing the substrate for D3 and all forms of vitamin D[19][62][75]. Low levels of vitamin D intensify age-related disease, e.g., immunosenescence and inflammaging [76]. Mg is also essential for a healthy gut microbiome [77], and a healthy gut microbiome promotes healthy aging [77]. The above-mentioned Mg-dependent functions support the view that Mg deficiency may drive the physiologic hallmarks of aging [9]. Mg deficiency profoundly affects oxidative stress and inflammaging [78], linked to aging [79][80], and increased intracellular Ca^{2+} [81]. This underscores the increased health risks associated with an imbalanced Ca^{2+}: Mg^{2+} ratio.

Interrelationship Between Calcium and Magnesium

Ca^{2+} and Mg^{2+} compete for the same calcium-sensing receptors (CaSRs) [82]. Although these receptors are found primarily in the parathyroid gland and kidneys, they are also present in other organs, including the alimentary canal [26]. Concomitant intake of Ca^{2+} and Mg^{2+} may lead to competition for these receptors. Synthesis and release of parathyroid hormone (PTH) require Mg. While the PTH response to plasma Ca^{2+} and Mg^{2+} is similar, it is much more sensitive to plasma Ca^{2+}. According to a 2018 study, reducing a high Ca^{2+}: Mg^{2+} ratio by increasing Mg intake significantly reduced circulatory 25(OH) D among those with serum levels of 25(OH) D close to 50 ng/mL [83]. Further study is warranted to determine whether this change is beneficial or detrimental.

When 25(OH) D levels are below 30 ng/mL, the demands of Mg-dependent 25(OH) D synthesis

surpass those of Mg-dependent PTH synthesis. Hypomagnesemia reduces the release and synthesis of hormones, especially PTH [84]. As Mg intake is increased, serum 25(OH) D levels also increase, up to about 25(OH) D levels 30 ng/mL, together with upregulation of Mg-dependent PTH synthesis. Beyond that, a further increase of the cellular Mg concentration results in downregulation of 25(OH) D. Increasing D3 to attain circulatory levels of 25(OH) D above 50 ng/mL, without first addressing an elevated Ca: Mg intake, may result in loss of Mg. Mg is consumed during the activation process of vitamin D metabolites [84]. In this study, BMI for both the study group and the placebo group averaged 30 kg/m. Consequently, fat cells may also have absorbed some 25(OH) D. All participants had Ca: Mg ratios well above 3.5 and would represent the right hypoparathyroidic wing of the bell curve (see Figure 2). This reflects the Western fast/processed food diet. These theoretical considerations are speculative and require clinical validation. Table 1 illustrates various combinations of Ca^{2+}: Mg^{2+} ratios.

Imbalance	Etiology	Reference
Hypocalcemia (low Ca: Mg)	Seen primarily with hypoparathyroidic conditions. Vitamin D deficiency, gut dysbiosis, and certain medications. Chronic kidney disorders (CKDs) that suppress glomerular filtration can elevate serum phosphate, a divalent anion that binds Ca and induces hypocalcemia. Mg insufficiency retards the synthesis of PTH and causes hypoparathyroidism.	[85]
Hypercalcemia (high Ca: Mg)	Primarily caused by overactive parathyroid glands, certain cancers, dehydration, and possibly prolonged excessive vitamin D intake (greater than 10,000 IUs/d).	[86][87]
Hypomagnesemia (high Ca: Mg)	Non-genetic origin: primarily encountered in those with low dietary intake, gut dysbiosis, or excess loss (excretion), e.g., vomiting or diarrhea.	[41]
Hypermagnesemia (low Ca: Mg)	Linked to CKDs, the primary culprit (other than iatrogenic). The low Ca: Mg seen in those on a traditional Asian diet is predominantly due to low Ca, not high Mg. CKDs associated with loss of glomerular filtration rate may not be able to maintain Mg homeostasis with resultant hypermagnesemia.	[31][88]

Table 1. Abnormal Ca: Mg ratios and their clinical settings

Symptoms of magnesium deficiency and an elevated Ca^{2+}: Mg^{2+} ratio can manifest in all three types of muscle: cramps in skeletal muscle, palpitations in cardiac muscle, and migraines and pre-menstrual syndrome (PMS) in smooth muscle. These two disorders and PMS have been linked to normo-magnesemic magnesium deficiency, first reported by Mansmann [89]. Like Ca^{2+}, Mg^{2+} is also essential for neural transmission. However, for other cell types, their functions are antagonistic: in smooth muscle cells, Mg^{2+}, a Ca^{2+} channel blocker, induces relaxation, while Ca^{2+} induces constriction.

An optimal balance of Ca^{2+} and Mg^{2+} is the target. Mg-dependent flavin adenine dinucleotide (FAD) and nicotinamide adenine dinucleotide (NAD), the active forms of vitamins B2 and B3, are vital to the electron transport chain in the Krebs cycle [90]. An elevated Ca^{2+}: Mg^{2+} ratio compromises glucose metabolism and increases mitochondrial dysfunction. Mitochondrial dysfunction, linked to inflammaging, involves an increase in intra-mitochondrial Ca^{2+} induced partly by the mitochondrial permeability transition pore [91].

Pathophysiology of Ca: Mg Ratio—Relevance to Global Health and Clinical Medicine

The Western diet typically has a high Ca-to-Mg ratio. Supplemental Ca was popular, especially among women, but this changed significantly after the Women's Health Initiative study [92] and similar studies published in subsequent years. As a result, the intake ratio increased from less than 2.5 to over 3.0, which is considered unphysiological [8]. Since Ca and Mg are ligands competing for the same Ca-sensing receptor (CaSR), it is unsurprising that their pathological ratios can adversely affect humans. CaSR is a G-protein-coupled receptor that detects extra-cellular Ca levels to maintain calcium homeostasis. Activation of the CaSR in parathyroid cells reduces the secretion of PTH, while activation in renal tubular cells promotes urinary excretion of Ca [93].

Considering the Ca: Mg ratio as a messenger (from the circulation to target cells would make it easier to understand its biological actions, particularly in target cells with high CaSR density, such as parathyroid cells, renal tubular cells, and the brain [94]. The calcium-to-magnesium (Ca: Mg) ratio is equally vital in maintaining systemic equilibrium [95]. A high Ca intake without adequate Mg can suppress PTH levels, negatively impacting bone remodeling and mineralization [95]. An imbalanced Ca: Mg ratio can also exacerbate chronic conditions, including cardiovascular diseases, due to improper Ca deposition in arterial walls [96]. Ensuring a balanced ratio, ideally around 2:1 (Ca: Mg), is critical to optimizing the synergistic effects of these minerals on vitamin D_3 metabolism, bone health, and overall physiological well-being [95] [97].

Other studies show that a high Ca: Mg ratio is associated with higher mortality in those with severe SARS-CoV-2 infections [98]. Others have reported that a high Ca: Mg ratio may be a biomarker of clinical outcomes for chronic disease, and rectifying it would derive benefit [99]. Both high and low Ca: Mg ratios are associated with higher cardiovascular and all-cause mortality [13]. Ca: Mg ratios >2.4 and <1.6 (iCa/iMg) are independently associated with increased risk of chronic conditions, like cardiovascular disease, cancer, metabolic syndrome, type 2 diabetes, as well as all-cause mortality in adolescents [100].

Optimal Calcium-to-Magnesium Ratio

The Ca^{2+}: Mg^{2+} intake recommendations are typically weight-to-weight (measured in mg/day). However, the interaction between these molecules occurs on an electrostatic molar basis, not a weight basis. When

laboratory data is involved, concentrations are usually converted from mg/dL to mmol/L to account for the molecular interactions. Determining ionized calcium (iCa^{2+}): ionized magnesium (iMg^{2+}) ratios is less straightforward, particularly in hospitalized patients, due to various factors influencing ionized levels. In addition, different studies use different methodologies, leading to confusion in interpreting the Ca^{2+}: Mg^{2+} ratio. Journal articles addressing the Ca^{2+}: Mg^{2+} ratio via these varying approaches contribute to this complexity.

The National Health and Nutrition Examination Survey (NHANES) from the Centers for Disease Control and Prevention (CDC) uses a detailed food frequency questionnaire (FFQ) to assess the national median Ca^{2+}: Mg^{2+} intake in mg/day from a civilian, non-institutionalized population [101]. The CDC's selection criteria are less stringent than those used to determine laboratory reference ranges. The recommended 1.7–2.6 (weight-to-weight in mg/day) reflects increased all-cause mortality in those outside this range [102]. One study from China involving 75,000 females and 62,000 males determined 1.7 as the lower limit for the range [103]. Another determined 2.6 as the upper limit for the range [104]. However, a later study conducted in a prostate, lung, colorectal, and ovarian cancer screening trial reduced the upper bound from 2.6 to 2.5 [105]

Two recent Chinese studies reported that this national intake ratio translated to actual serum reference ranges in mmol/L for Ca: Mg in a healthy subset of this population between 2.4 and approximately 3.6 [103] [104]. These Chinese serum mmol/L levels, with 70% of Mg unbound and 50% of calcium unbound, translate to a Ca^{2+}: Mg^{2+} ratio between 1.7 and 2.5, closely replicating the recommended 1.7–2.6 weight-to-weight intake. Using accepted laboratory reference ranges for total serum Ca and Mg in mmol/L, the American mean for iCa^{2+}: iMg^{2+} is similar (1.66–2.51). By comparing the reference range values for total serum Ca and Mg with their reference ranges for iCa^{2+} and iMg^{2+}, for alignment, Ca^{2+} must make up about 50% of total serum calcium, and Mg^{2+} must make up about 70% of total serum magnesium. Therefore, the recommended 1.7–2.6 range for Ca^{2+}: Mg^{2+} intake (weight-to-weight, as determined by FFQs) closely approximates the recommended range for serum Ca^{2+}: Mg^{2+} (mmol to mmol).

Calcium-Magnesium Balance in Disease States

Mg deficiency and an elevated Ca^{2+}: Mg^{2+} ratio are linked to inflammaging and oxidative stress. Inflammaging and oxidative stress, in turn, are linked to cancer [105], dementia [106], cardiovascular [107], diabetes [108], autoimmune disease [109], and obesity [17]. Not surprisingly, the Ca^{2+}: Mg^{2+} ratio may predict

cancer, metabolic disease, infections, autoimmune diseases, and obesity [110]. However, many reports on the relationship between Ca and cancer and Mg and cancer are contradictory. Nevertheless, when these reports include this balance, relationships become clearer. If the Ca^{2+}: Mg^{2+} ratio is balanced with euparathyroidism, Ca and Mg levels must also be sufficient (see hypothetical Figure 2).

Cancers, and Ca^{2+}: Mg^{2+}

An imbalanced Ca: Mg increases cancer risks when Ca is low (decreased ratio) and Mg is low (increased ratio). Ca and Mg compete for the same Ca-sensing receptor (CaSR). Many clinical studies have documented this for cancers of the colorectum [110], esophagus, prostate, lung, breast, ovary, and pancreas. (see Table 2).

Ca: Mg	Clinical Outcomes	Reference
Increasing Ca intake when Ca: Mg is low	Decreases the risk of colorectal cancer	[111][112]
Increasing Ca intake when Ca: Mg is high	Does not decrease the risk of colorectal cancer	[112]
Increasing Ca intake when Ca: Mg is low (less than 1.7)	Decreases esophageal cancer risk	[113]
Increasing Mg intake when Ca: Mg is low (less than 1.7)	Increases esophageal cancer risk	[113]
Increasing Mg intake when Ca: Mg is high	Decreases the risk of prostate cancer	[114][115]
A high or low Ca: Mg	Increases the risk of lung cancer	[115][116]
A high Ca: Mg	Decreases survival in breast and ovarian cancer	[117][118]
Increasing Mg when Ca: Mg is high	Decreases breast cancer risks	[119]
Increasing Ca when the Ca: Mg is low	Decreased risks for pancreatic cancer	[120]
Increasing Mg when Ca: Mg is high	Decreases the risks of pancreatic cancer	[121]

Table 2. Examples of different combinations of Ca” Mg ratios and reported clinical correlations

Metabolic Disease and Ca^{2+}: Mg^{2+}

The balance between Ca^{2+} and Mg^{2+} plays a critical role in metabolic disease, with an imbalanced Ca^{2+}: Mg^{2+} ratio (either high or low) contributing to various metabolic disorders [122]. Elevated Ca^{2+} levels in the presence of low Mg^{2+} may manifest insulin resistance, impaired glucose metabolism, and increased risk for type 2 diabetes [122]. Furthermore, the dysregulation of this ratio exacerbates inflammation and oxidative stress, which are common pathophysiological features in metabolic diseases, including obesity and cardiovascular conditions [123].

Research suggests that maintaining an optimal Ca^{2+}: Mg^{2+} ratio could help mitigate these conditions and improve metabolic function by enhancing insulin sensitivity and reducing systemic inflammation. For instance, studies have highlighted the protective effects of Mg in preventing metabolic syndrome, emphasizing the need for proper Mg^{2+} intake alongside Ca to maintain metabolic health [124][125]. Some specific examples appear below.

Insulin Resistance, Diabetes Mellitus, and Ca: Mg

The growing global incidence of insulin resistance plays a key role in the development of type 2 diabetes, cardiovascular diseases, and obesity-related conditions [126][127]. Serum Mg levels may contribute to this increasing prevalence. The laboratory reference range for total serum Mg is typically 0.75-0.95 mmol/L. A study involving 10,000 participants showed that the risk for diabetes mellitus increased by 20% when serum Mg was between 0.80-0.85 mmol/L and 50% when it was between 0.75-0.80 mmol/L [128]. Additionally, conditions like PMS and migraine headaches may reflect normo-magnesemic Mg deficiency, also known as chronic latent magnesium deficiency (CLMD), which may correspond to levels in the 0.75-0.85 mmol/L range. Table 3 summarizes the risks and benefits of Ca to Mg ratios in common disorders [58] [89]. Insulin resistance links all entities in Table 3, including many other cancer types. If the lower limit of serum Mg were to be raised to.85 mmol/L, the recommended Ca: Mg range would shrink to 1.7-2.3.

Disorder	Clinical Presentations
Cardiovascular Disease	Elevated dietary Ca: Mg intake increases the risk for CVD [11]. Other researchers have reported that elevated serum Ca: Mg predicts mortality in CVD [12][13]. Low or high Ca intake increases cardiovascular disease risks when Ca: Mg is outside 2.0-2.5 [129].
Dementia	Both low Ca and Mg are associated with cognitive decline [130] and dementia [131]. Low Ca in Chinese is linked explicitly to dementia [132], while low Mg in Americans is specifically linked to dementia [14][15]
Obesity	Low dietary Mg intake is associated with higher BMI and obesity [16]. Obesity induces a low-grade, diffuse, pro-inflammatory state [17].
Cancer	Risks for numerous cancers increase when Ca intake is low and Ca: Mg is low or when Mg intake is low and Ca: Mg is high. Similarly, risks decrease when Ca: Mg is low and Ca intake is increased or when Ca: Mg is high, and Mg intake is increased [18][110][113][114][117][118][119][120][121][133].
Autoimmune Disease	Mg deficiency increases the risk for post-COVID syndrome [134], recovery from infections [47], and rheumatoid arthritis and lupus [135][136].
Infectious Disease	Mg deficiency increases mortality risks for COVID-19 [47].

Table 3. Examples of disorders linked to an imbalanced Ca: Mg

Infectious and Autoimmune Diseases and Ca: Mg

Mg deficiency has been associated with T-cell dysfunction, which can impair resistance to viral and bacterial infections [137]. However, the impact of Mg deficiency on vitamin D synthesis may have an even more profound effect. Vitamin D receptors (VDRs) are present in virtually all cells, and Mg deficiency can hinder vitamin D activation, further contributing to immune system dysfunction. T-cell dysfunction may induce autoimmune diseases. Adequate dietary and supplemental Mg intake may reduce all-cause mortality in individuals with rheumatoid arthritis [138].

Mg deficiency increases the risk of rheumatoid arthritis [135], and oral Mg supplementation may reduce pathogenic autoantibodies and skin disease severity in murine lupus models [136]. Post-COVID syndrome, now recognized as an autoimmune condition by the Autoimmune Registry, may also reflect Mg levels.

Total serum Mg level below 0.80 mmol/L increased COVID-19 mortality by 29% and the risk of developing post-COVID syndrome by 114% [47], potentially reflecting CLMD. In conclusion, Mg deficiency negatively affects immune regulation while exacerbating inflammation, infectious diseases, cancer, and metabolic/autoimmune disorders [47][121][139]. A low calcium-to-magnesium (Ca: Mg) ratio increases sickle cell disease sickling [140].

Mechanisms Underlying Calcium and Magnesium Imbalance

Multiple factors contribute to an imbalanced calcium-to-magnesium (Ca: Mg) ratio, including deteriorating agricultural soil, reduced essential mineral content in vegetables, and the global rise in consumption of processed foods and phosphate-rich soft drinks [96][140]. These dietary patterns are also associated with compromised gut microbiome diversity and function, further impairing nutrient absorption and metabolism [96][141][142]. An imbalanced Ca: Mg ratio is frequently a surrogate marker for vitamin D insufficiency or deficiency, as Mg is essential for synthesizing and activating vitamin D [142][143]. Furthermore, Mg deficiency often goes undetected because routine serum Mg testing is uncommon and, even when done, does not reflect total body stores, making it easy to overlook [99][144].

The situation compounds socioeconomic disparities and cultural practices that influence diet [145][146], clothing habits that limit sun exposure, and uneven access to healthcare services [147][148][149]. Besides, individuals from low-income or traditional communities often face limited dietary diversity and reduced availability of nutrient-rich foods, heightening their risk for micronutrient imbalances [150]. Aging and elevated body mass index (BMI) contribute to chronic low-grade inflammation, insulin resistance [151][152], and micronutrient depletion, exacerbating the health consequences of an imbalanced Ca: Mg ratio [153]. A widespread lack of public awareness and the absence of routine clinical screening for Mg status obstruct early detection and effective prevention. Figure 2 illustrates the proposed mechanisms linking circulating 25(OH) D levels with Ca: Mg ratios.

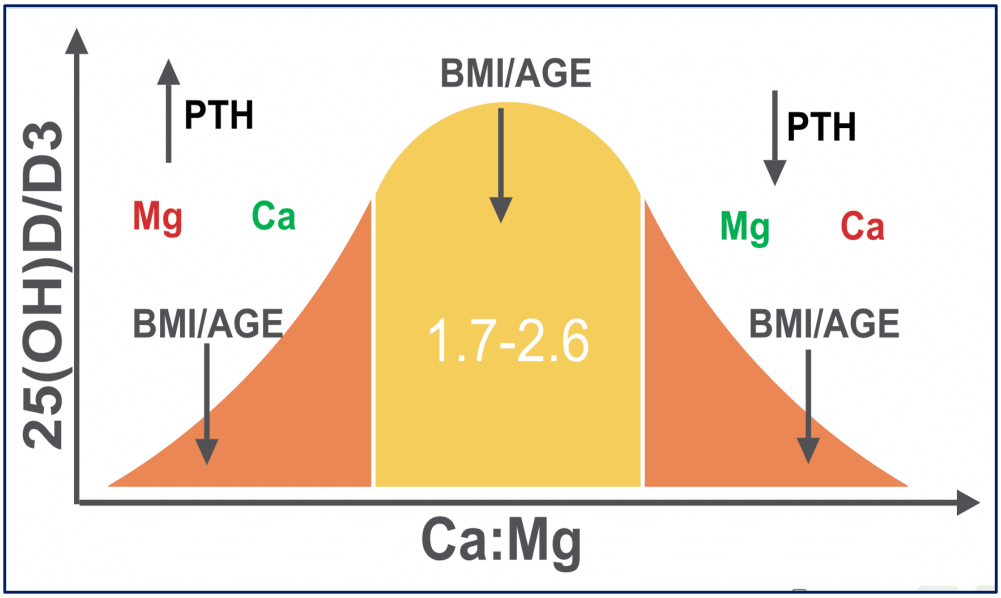

Figure 2. A hypothetical figure that illustrates improving Ca: Mg and BMI may enhance the efficacy of D_3. If Ca: Mg is optimal, attaining 25(OH) D >50 ng/mL may be theoretically possible with 2000 IUs of D_3 supplementation. Optimal Ca: Mg should also reflect the euparathyroid state and sufficiency of Ca and Mg. One study suggests that the upper limit of optimal Ca: Mg be reduced to 2.5 [129].

Notably, PTH regulates Ca and Mg similarly, but Ca is the primary determinant of PTH level. Besides, Ca and Mg are antagonists in many ways, e.g., Mg is a Ca channel blocker, and both compete for the same CaSR. The left side of the bell curve in Figure 2 represents the established inverse relationship between serum 25(OH) D and parathyroid hormone (PTH). A diet low in Ca, thus, a low Ca: Mg ratio—such as a traditional Asian diet—stimulates PTH secretion. However, increasing Ca intake to rectify the imbalance downregulates PTH/vitamin D synthesis and Mg absorption in those already D_3-deficient. This might increase the need for higher D_3 and Ca supplementation to achieve optimal 25(OH) D concentrations, at the expense of Mg.

In contrast, the right side of the bell curve in Figure 2 reflects scenarios common in Western diets, characterized by high Ca intake and routine D_3 supplementation without adequate Mg. In this context, Mg intake is often insufficient to support optimal PTH synthesis. Consequently, D_3 supplementation alone may downregulate Mg-dependent PTH, perpetuating a hypo-parathyroid state. This suggests that individuals with a suboptimal (high) Ca: Mg ratio may require even higher D_3 and Mg doses to achieve target 25(OH) D levels.

Complex pathophysiological interactions related to Ca: Mg ratios

As previously discussed, a 2018 study [83] reported that when baseline 25(OH) D exceeded 35 ng/mL, Mg supplementation (e.g., 200 mg/day) surprisingly reduced 25(OH) D synthesis [83]. However, that study did not assess PTH. Further analysis showed that Ca: Mg intake ratios (mg/d) were 3.9 and 3.7 in the placebo and treatment groups, respectively. Both groups were also overweight or obese [83]. These findings suggest that when Ca: Mg is elevated, Mg supplementation goes first to vitamin D synthesis and then to PTH synthesis. Another study supports this interpretation, proposing that in overweight and obese individuals with elevated Ca: Mg, increased Mg intake may first restore PTH synthesis [154]. The Ca: Mg ratio must normalize before more Mg is available for 25(OH) D synthesis sufficient to reach 50 ng/mL.

These studies support the proposed bell curve in Figure 2, placing participants from both studies on the right wing [83][154] of the bell. Both findings suggest that near the lower limit of serum Mg^{2+} at 0.54 mmol/L, Mg^{2+} levels may be insufficient for adequate PTH synthesis. The lower reference value of total serum Mg at 0.75 mmol/L corresponds to a Mg^{2+} of approximately 0.52 mmol/L. Optimal allocation of Mg^{2+} for effective 25(OH) D synthesis may require Mg^{2+} levels approaching 0.60 mmol/L. Multiple studies recommend increasing the lower reference threshold for total serum Mg from 0.75 to 0.85 mmol/L [37][102][155], corresponding to a Mg^{2+} of approximately 0.60 mmol/L. As previously stated, this would lower the recommended upper limit for iCa: iMg from 2.6 to 2.3.

Clinical Implications and Recommendations

An optimal Ca: Mg ratio works synergistically with vitamin D. While a serum 25(OH) D level of 30 ng/mL may suffice for skeletal health, a target of 50 ng/mL is necessary to support extra-skeletal functions, which are intracellular. Intracellular Mg^{2+} concentrations consistently exceed those of extra cellular Mg^{2+}. Both ionized Ca and Mg are integral to cellular signaling and are essential for regulating diverse cellular functions and enzymatic processes, including ion channel activity, metabolic pathways, and intracellular signaling mechanisms [156].

A study on FFQs in individuals not taking supplements found that a Ca: Mg ratio between 2.2 and 3.2 offered the greatest protection against osteoporosis [36][95]. While FFQ-derived data generally suggest an ideal Ca: Mg range of 1.7 to 2.5, the higher range recommended for skeletal (primarily, extra cellular) health implies that additional Mg may be needed for extra-skeletal (intracellular) functions of target cells—such as intracellular signaling [157], including in cardiovascular and immune cells [158][159]. Adequate Mg is

indispensable in this context, and a balanced Ca: Mg ratio enhances the effectiveness of 25(OH) D as well as key enzymatic processes (see Figure 2). Besides, Mg supplementation when Ca: Mg is elevated, and 25(OH) D exceeds 30 ng/mL may be less effective [83].

A. Overlooked Physiological Roles of RBC Magnesium

Durlach first published his 2:1 weight-to-weight recommendation for Ca: Mg intake in 1989 [1][2]. The medical literature and median laboratory reference range values for physiologic serum iCa and iMg support this. In addition, the molecular weight of Ca is nearly twice that of Mg [23][24]. However, unlike Ca, Mg occupies both intravascular compartments—plasma and RBCs, i.e., RBC Mg, a recent development. Serum measurements of Mg do not include RBC Mg. Recommended RBC Mg concentration (the reservoir maintaining plasma iMg homeostasis) is about three times that of plasma Mg [37]. Comparison of Chinese and American reference range means for whole blood Mg versus plasma Mg supports this multiple.

Mg-dependent PTH responds more to circulating iCa than iMg, and because iCa and iMg are often competitors, a conflict of interest may develop. High Ca intake translates to low PTH, low endogenous D, and low Mg. Low Ca intake translates to high PTH and high endogenous D, but only if Mg is sufficient. Low Mg intake may compromise the health benefits of vitamin D. The RBC reservoir of Mg may counterbalance this. If one adjusts the 2:1 Ca: Mg weight-to-weight recommendation of Durlach for differential molar weights (40:24) and dissociation constants (50% v 70%), then this weight-to-weight ratio should be 2.33. However, if Ca: Mg is balanced (euparathyroidism), then this balance should optimize vitamin D. Vitamin D enhances intestinal absorption/renal resorption of Ca. This might lower the intake ratio and more closely reflect Durlach's 2:1 recommendation. Nevertheless, is that ratio physiologically correct?

Using median laboratory reference range values for serum Ca (9.5 mg/dL), serum Mg (2.0 mg/dL) [37][82] [133], and that recommended for RBC Mg (6 mg/dL) [37] and assuming 40% hematocrit and five liters blood volume, one can show that to maintain homeostasis (physiologic 2:1 ratio of serum iCa: iMg with adequate RBC reservoir), absorption of Ca: Mg should theoretically yield about 3:2 weight to weight (285 mg Ca: 180 mg Mg). NHANES (FFQs) data through 2023 indicate that the intake ratio has exceeded 3:1 since the year 2000.

However, determining the general Ca: Mg intake ratio required to meet this theoretical 3:2 need and to maintain Ca: Mg homeostasis/euparathyroidism is intake-determined but absorption-dependent. For example, if about 30% of Ca and 35% of Mg were absorbed, then intakes of 950mg Ca and 514mg Mg,

nearly 2:1, would be required to meet the theoretical need. If sufficient vitamin D were aboard and absorption were equivalent, then intakes of 800 mg Ca and 514mg Mg, nearly 3:2, would be required. Since they compete for the same CaSR absorption receptors, temporal separation of Ca and Mg intake should also impact absorption.

A 3:2 intake ratio of Ca: Mg seems optimal for sufficient vitamin D, otherwise healthy individuals following a Western diet (hypoparathyroid). A 1:1 ratio might be considered initially for those with Ca: Mg > 2.6 (hypoparathyroid). Ca is often high in processed foods and carbonated colas, which are part of Western diets. Targeting a 2:1 intake ratio might be more appropriate in those on traditional Asian diets low in Ca (hyperparathyroid). The 3:2 ratio may also help address CLMD (e.g., pre-menstrual syndrome/migraines [89] and early insulin resistance [128], conditions prevalent among those consuming a Western fast-food diet. Much has changed since 1989. Deteriorating diets and lifestyle changes have conspired to compromise both intake and absorption. These conclusions, however, are theoretical and require clinical validation.

B. Physiological vs. Pathological Ca: Mg Ratios

Escalating BMI remains a central issue—sufficient attention to exercise and diet is necessary to lose weight [160][161]. A diet high in leafy greens, nuts, seeds, and legumes supports better Mg status, though supplementation is often necessary. To avoid the laxative effect—especially from Mg citrate—use varied forms in divided doses. Synbiotics may further support Mg absorption by improving gut microbiome health. Pyridoxal phosphate (active vitamin B_6) [162]—not its inactive form, pyridoxine—enhances Mg uptake. Excess pyridoxine can competitively inhibit pyridoxal phosphate [163]. Notably, elemental Mg typically constitutes no more than 10% of the weight per tablet in most supplements.

Compared to CRP, Ca: Mg is a more specific and actionable indicator of inflammaging and oxidative stress, both linked to cancer, metabolic diseases, infections, autoimmune disorders like post-COVID syndrome, and obesity. While assessing dietary intake of either Ca or Mg is challenging, obtaining relevant laboratory data is straightforward. Mg is essential for many physiological functions. Nevertheless, for over 50% of Americans, intake is insufficient [37].

Synthesis of D3/25(OH) D/1,25$(OH)_2$ and binding to VDBP require Mg [96]. Therefore, it is crucial to ensure that individuals consume the recommended amount of Mg to optimize vitamin D benefits and support all body systems [83][96]. Unfortunately, measuring serum Mg is not routine, as it is not included in standard

panels, requiring specific requests. If Ca: Mg is balanced, then each is within normal limits: i.e., an euparathyroid state exists (see Figure 2).

Human physiological demands have not changed. China and America share similar long-standing reference range limits for both Ca and Mg. Nevertheless, PTH laboratory reference ranges differ – 10-65 pg/mL in America versus 10-100 pg/mL in China [106]. This is due to the relative availability/intake of critical micronutrients influenced by cultural, agricultural, and food habits considerations. The shortfall in Mg is global, albeit much more so on a Western diet. However, wealthy Western countries are ingesting too much Ca, and the rest of the world is taking too little. The latter is better known, but the former is not so well known.

C. The Impact of Maintaining Physiological Ca: Mg Ratio on Public Health

Magnesium is essential for enzymes involved in synthesizing and activating vitamin D 25(OH) D and calcitriol, enhancing receptor binding, as well as for G-protein signaling, CYP450 activity, B-vitamin activation, epigenetic methylation, glucose metabolism, and mitigating oxidative stress associated with aging. Maintaining a balanced Ca-to-Mg intake ratio—ideally between 1.7 and 2.6 (weight-to-weight)—is fundamental to optimizing vitamin D metabolism and supporting broad systemic health. Disruptions to this ratio are likely to impair vitamin D efficacy and elevate the risk of chronic diseases and conditions, including cancer and cardiovascular conditions, as well as dementia and post-viral syndromes [110]. Notably, a Ca: Mg ratio outside the optimal range has been linked to a greater prevalence of these issues, while adjusting it via magnesium supplementation has been shown to improve vitamin D status and cognitive function in randomized trials [14][110].

From a public health perspective, targeting an optimal Ca: Mg ratio is a practical and highly cost-effective, globally scalable strategy to reduce chronic disease burden. Data from NHANES indicate that many individuals in the U.S. already exceed a Ca: Mg ratio of 3.0, mainly due to high calcium and low magnesium intakes—a trend that correlates with worsening metabolic and cardiovascular outcomes [99]. Moreover, in bone health studies [95], individuals with a Ca: Mg intake ratio of around 2.8 demonstrated significantly higher bone mineral density compared to those with lower ratios. These findings suggest that public health policies should emphasize correcting mineral imbalances—through dietary guidance, fortified foods, and supplementation—to improve outcomes across various domains, including metabolic health, cognitive function, and longevity [95][99].

D. Expanded Knowledge Contributions by This Manuscript

This Perspective highlighted the importance of maintaining an optimal dietary calcium-to-magnesium (Ca: Mg) ratio—targeted between approximately 1.7 and 2.6, as a critical global public health issue [36]. It underpins efficient vitamin D metabolism and supports a wide range of physiological processes [164]. Magnesium is indispensable for the enzymatic activation of vitamin D in the liver and kidneys, enhancing receptor binding and downstream benefits for bone, metabolic, and immune health [164].

Furthermore, this study illustrates that a balanced Ca: Mg ratios contribute to proper G-protein–coupled receptor function, CYP450 enzyme activity, epigenetic regulation, glucose metabolism, and control of oxidative stress and chronic inflammation. Disruption of this balance is implicated in elevated risks of cancer, cardiovascular disease, dementia, post-viral syndromes (including post-COVID conditions), and type 2 diabetes—conditions that burden global health systems. Laboratory data, large-scale epidemiological observations (e.g., NHANES), and emerging cohort studies corroborate these associations, highlighting the need for clinically validated guidelines.

Beyond its clinical implications, the manuscript advances public health knowledge by positioning Ca: Mg optimization as a cost-effective, globally relevant strategy for chronic disease prevention. NHANES analyses show that U.S. adults have had mean Ca: Mg intake ratios >3.0 since 2000, and a ratio-based guidance of ~1.7-2.6 has been proposed to support metabolic and bone health [99]. Correcting high Ca: Mg ratios has been associated with better health and vitamin D utilization in a randomized trial, lower systemic inflammation in meta-analyses, and improved brain structure/function in population studies of aging [83][99][165]. These are substantiated by illustrating Mg supplementation significantly reduced inflammatory markers like plasma fibrinogen, tartrate-resistant acid phosphatase type 5, tumor necrosis factor-ligand superfamily member 13B, ST2 protein, and IL-1 [83][166]. In conclusion, Mg supplementation significantly reduces different human inflammatory markers, in particular serum CRP and nitric oxide levels, aiding better health outcomes [83]. For example, calcium intake is inversely associated with CRC (P_{trend} .03) when the Ca: Mg ratio is maintained between 1.7 and 2.5 [110].

These findings challenge calcium-centric recommendations: the Ca: Mg ratio modifies associations with colorectal neoplasia, and reducing the ratio to ~2.3 via magnesium improved vitamin D status in trial settings [95][110]. From a population health perspective, optimizing the Ca: Mg ratio represents an affordable, scalable strategy to prevent chronic disease and enhance metabolic resilience [166]. For example, higher dietary Ca: Mg ratios have been linked with increased risk of non-alcoholic fatty liver

disease [95], while prospective cohort data show that individuals—particularly men—with Ca: Mg ratios above 1.7 benefit from reduced all-cause and cardiovascular mortality when calcium and magnesium intake is sufficient [99][166].

Additionally, elevated magnesium intake, especially when combined with adequate vitamin D, is associated with reduced risk of vitamin D deficiency and may modify mortality outcomes in large population-based studies [95]. These findings underscore the manuscript's novel contribution: illuminating the Ca: Mg ratio as a pivotal determinant of public health, beyond isolated mineral intake, and advancing the imperative for dietary policy and clinical practice to incorporate this nuanced perspective. Increased dietary Mg intake also improves brain health in the general population, particularly in women [165]. Table 4 summarizes the importance of maintaining a physiological Ca: Mg ratio between 1.7 and 2.6.

Benefiting tissue or system	Specific benefit from maintaining the physiological ratio of Ca: Mg
Vitamin D and the skeletal system	Maintaining the above-mentioned balanced Ca: Mg ratio optimizes vitamin D and skeletal metabolism, immune function, and systemic health.
Increase the risks of several chronic disorders	Higher Ca: Mg ratios (>3.0), common in many populations, are linked to higher risks of cancer, cardiovascular disease, diabetes, neurodegeneration, and worse infectious disease outcomes.
An explanation for the vitamin D replacement clinical trial outcomes	Most vitamin D studies overlook magnesium status (failure to replace Mg in deficiency) and Ca: Mg balance, which may explain conflicting results in supplementation trials.
Lowers inflammation and improves multiple body system functions	Optimizing the Ca: Mg ratio improves vitamin D efficacy, lowers inflammation, and supports bone, metabolic, and cognitive health.
A broader recommendation	Public health guidelines should shift from focusing on calcium intake alone to Ca: Mg ratio-based recommendations for preventing chronic disease and reducing healthcare costs.

Table 4. Specific reasons and benefits of maintaining the physiological Ca: Mg ratios

Conclusion

Maintaining an optimal calcium-to-magnesium (Ca: Mg) ratio is crucial for numerous physiological functions and for preventing chronic and infectious diseases. An imbalanced ratio—below 1.7 or above 2.6—may prompt increased risks of cancer, cardiovascular disease, neurodegenerative disorders like dementia, autoimmune conditions such as post-COVID syndrome, and greater susceptibility to infections. Rising body mass index (BMI), which influences and is influenced by Ca: Mg imbalance, may further heighten these risks. Some meta-analyses report no benefit from D3 supplementation when 25(OH) D levels exceed 30 ng/mL. Unfortunately, these meta-analyses do not include Mg or Ca: Mg status.

If 30 ng/mL of 25(OH) D is sufficient for skeletal (endocrine) needs, despite Ca: Mg imbalance and parathyroid dysfunction [83][155], then additional supplemental D3 might provide even greater benefit when 25(OH) D > 30 ng/mL and 1.7 < Ca: Mg < 2.6 with euparathyroidism. Optimum Ca: Mg improves extra-skeletal health (see Tables 2,3). This feature is not dependent on the endocrine (hormonal) role of vitamin D but on its intracrine role, suppressing inflammaging and improving systemic immunity. This requires higher doses of D_3, enough to reach 50 ng/mL 25(OH) D. Meta-analyses that refute this benefit overlook the key role Ca: Mg plays in the body's ability to synthesize and utilize vitamin D, whether from solar UVB exposure or supplementation with cholecalciferol (D_3), impacting metabolic regulation.

Furthermore, outside this recommended Ca: Mg range, other benefits are lost, e.g., the anti-cancer benefits of physical activities [164][167]. Symptoms of aging other than cancer, e.g., dementia, CVD, autoimmunity, infections, and obesity, intensify. Many of these symptoms mimic those of Mg deficiency. Given the complex roles of these minerals in health and disease, further research should explore their interactions and establish evidence-based clinical guidelines for optimal intake and monitoring.

Statements and Declarations

Conflicts of Interest

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Data Availability

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