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REVIEW

Ageing, Nutrition, and Infection: The Forgotten Triad

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Abstract

Ageing is a complex sociocultural and physiological process characterised by declines in nutritional and functional status and the immune response. The ageing immune system is plagued by both quantitative and qualitative deficits in the innate and adaptive immune system characterised by reduced responsiveness to de novo antigens and vaccines, along with low-level inflammation which is modulated by nutrition. In this short review, we will highlight the vicious cycle of infection and malnutrition, which is prevalent in the elderly. In doing so we will highlight the relevant contributions of both macronutrient and micronutrient deficiency to immune system dysfunction highlighting the need to research and modify nutrition in the elderly to improve health-related outcomes and protect healthcare systems from anticipated rises in the ageing population.

Key words: nutrition; ageing; immunosenescence; infection; micronutrients; illness

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Introduction

By 2050, there will be approximately 2 billion elderly people (≥60 years old) worldwide (Kaur et al, 2019; World Health Organization, 2024). Ageing therefore represents a significant global health challenge due to its association with physiological decline and the emergence of both non-communicable and infectious disease risk (Chen et al, 2021). This decline is underpinned by changes in both nutritional status and the structure and function of the immune system of the elderly. Malnutrition refers to the disequilibrium between nutrient intake and demand. Globally, malnutrition is a concerning problem with a recent modelling analysis estimating 5 billion people to be affected by at least one or more micronutrient deficiency of which iodine, calcium, vitamin E and iron are amongst the most prevalent with clear regional gender imbalances existing (Passarelli et al, 2024). Moreover, the prevalence of malnutrition significantly increases with age and setting with 50.5% of elderly patients in healthcare facilities malnourished making this a key public health concern (Chen et al, 2021; Ma et al, 2024). The cause of malnutrition in the elderly is convoluted and often multifactorial involving psychosocial, physiological and functional factors (Chen et al, 2021; Salazar et al, 2020). Malnutrition manifests in the elderly individual in many forms including delayed wound healing and recovery from illness, muscle catabolism leading to sarcopenia and exacerbation

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of the age-related decline of multiple components of the immune system manifesting as increased infection incidence and infection-related mortality (Cristina and Lucia, 2021; Ma et al, 2024). This culminates in the development of 'frailty' a state of vulnerability that increases the risk of disability, hospitalization, and mortality (Tran Van Hoi et al, 2023; Rolf et al, 2022). In this short review, we will consider the physiological underpinnings of this complex interaction between nutrition and infection risk in the ageing individual and in doing so describe suitable nutritional countermeasures which may forestall this decline and improve immune function and prevent frailty. This is made increasingly relevant due to the projected increases in the global elderly population at a time of increasing austerity.

The Ageing Immune System

The immune system is a complex interplay between multiple immune cells, physical barriers, secretions and proteins, which function to prevent invasion by pathogens and subsequent infection development. Innate immune cells, e.g., neutrophils and macrophages, function to identify pathogens via conserved interactions between their pathogen-recognition-receptors and pathogen-associated-molecular-patterns with subsequent recruitment of other innate cells culminating in phagocytosis, degranulation and pathogen destruction. Macrophages and dendritic cells also have the ability to prime the adaptive immune system (T-cells, B-cells) through antigen presentation, leading to their proliferation, effector function and persistence in the form of immunological memory (Fulop et al, 2023; Kim et al, 2022; Maggini et al, 2018). For the immune system to function, it requires energy from and is modulated by macronutrients and micronutrients. Without these, immune dysfunction occurs, infection risk rises, and catabolism ensues. This effect is further amplified in the elderly, in whom immunosenescence occurs (Tran Van Hoi et al, 2023; Marcos et al, 2003).

With advancing age, the immune system changes, becoming less efficient at responding to new pathogens, with innate immune cells becoming inherently less responsive, cytotoxic, migratory, and able to present antigens (Chandra, 2002; Maggini et al, 2018; Simon et al, 2015). Anatomical barriers also suffer with reduced barrier function and regenerative capacity, alongside declines in mucociliary clearance, urinary flow, gastric pH and secretory immunoglobulin A (IgA) production. In the presence of comorbidities, these changes are accelerated and lead to relative immunosuppression and increased infection risk (Esme et al, 2019; Walrath et al, 2020).

Importantly, with age significant declines in the adaptive immune system occur, with diminished naïve T- and B-cells output due to thymic atrophy and declining haematopoietic stem cell (HSC) number. This leads to a reliance on pre-existing memory T- and B-cells synonymous with immunological imprinting manifesting as reduced responses to new infections and vaccination. Correspondingly, due to altered T-cell homeostasis and tolerance increased rates of autoimmunity and reactivation of latent viral infections (e.g., cytomegalovirus) are observed (Maggini et

al, 2018; Ray and Yung, 2018; Simon et al, 2015). These changes to the immune system underpin immunosenescence.

Immunosenescence therefore is an age-related phenomenon which involves multiple components of the immune system becoming dysfunctional and less reactive to infectious stimuli. Chief among these changes include thymic involution which begins as early as 1 year of age and accelerates in later life with CD4+ and CD8+ T-cell output decreasing approximately 100-fold between the ages of 20 years and 70 years old (Fulop et al, 2023; Liang et al, 2022). This decrease is triggered and sustained by thymic inflammation, systemic stress and declines in key molecules of thymic gland regeneration and maintenance (e.g., Forkhead box N1 (FOXN1)) which are seen with ageing (Fulop et al, 2023; Liang et al, 2022). Mirroring thymic atrophy are reductions in HSCs number, which leads to decreased production of immune cells with a skewed predisposition for myeloid progenitor cell differentiation, whose products in particular macrophages are defective as described (Li et al, 2023b). This decline in HSC reserve is accelerated by systemic inflammation and is the basis of immunosenescence.

With ageing cells become senescent and in doing so demonstrate altered behaviour including cell-cycle arrest, resistance to apoptosis, mitochondrial dysfunction leading to aberrant stimulation of pathogen-recognition-receptors, reactive oxygen species (ROS) formation and decreased autophagy. This helps to explain the links between ageing and both infection and cancer risk. Immune cells are not exempt from this, and this contributes to the qualitative and quantitative changes noted to their function with age (Fulop et al, 2023; Ray and Yung, 2018; Simon et al, 2015).

As a result of senescence, there is a build-up of damage in host proteins and in particular deoxyribonucleic acid (DNA) through mutations, epigenetic changes and telomere dysfunction. In doing so this cellular 'waste' builds-up and serves as antigens for the immune system and in particular macrophages leading to a state of chronic immune activation termed 'inflammaging' resulting in elevated levels of pro-inflammatory cytokines and proteins including interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), IL-1β and C-reactive-protein (CRP). This complements augmented cytokine release from senescent cells termed senescence-associated secretory phenotype. Indeed, this dyscytokinaemia and pro-inflammatory state has been demonstrated albeit at a reduced state in healthy centenarians compared to younger elderly adults highlighting the prospect of healthy ageing (Dugan et al, 2023; Li et al, 2023b). Given the importance of macrophages and dendritic cells in T-cell development through appropriate antigen presentation via autophagy, T-cell responses are further abrogated as part of immunosenescence (Dugan et al, 2023; Li et al, 2024; Liu et al, 2023; Tabibzadeh, 2023).

Therefore, immunosenescence driven by inflammaging functions as a low-grade inflammatory process and helps drive in ageing, infection incidence, chronic disease progression (e.g., neurodegenerative), cancers, metabolic disease, sarcopenia and finally frailty. Indeed, serum CRP and IL-6 can be used as a biomarker of frailty (Tran Van Hoi et al, 2023; Ma et al, 2024).

Importantly, immunosenescence can be modulated by nutrition as observed by reductions in several inflammatory mediators including CRP, IL-6 and intercellular adhesion molecule (ICAM-1) which mediates immune cell organ infiltration with the traditional Mediterranean diet (Aiello et al, 2019). Of micronutrients, which modify immunosenescence, zinc deficiency in particular has been shown to accelerate both thymic atrophy through reduced thymulin production and altered immune cell signaling and behaviour (e.g., increased apoptosis) and has been linked with an increased infection incidence (Prasad, 2008). Other key nutrients include vitamin C, which helps to maintain physical barriers through collagen synthesis and connective tissue regeneration while serving as an antioxidant and thereby helping to limit macrophage-mediated tissue damage associated with inflammation. Similar actions have been found with vitamin D, which can modulate B, T and natural killer (NK) cell replication and function with deficiency linked with reduced vaccine responsiveness in elderly patients and thus if replete could potentially forestall the effects of immunosenescence (Calder et al, 2022; Giustina et al, 2023). The gut is the boundary between exogenous material (e.g., food) and the host, which provides a significant route for infection development and an important means by which normal development of the immune system occurs. It is for this reason that 70% of all immune cells are resident within the gut organised in the form of gut-associated lymphoid tissue including lymphoid follicles and peyer patches consisting of populations of macrophages, dendritic cells, B- and T-cells, plasma cells and NK cells (Calder et al, 2022).

Throughout life, the gut microbiome, which includes bacteria, fungi and viruses evolves and serves as an educator to the immune system and works symbiotically with the human host. This is evidenced by the diffuse deleterious effects to the immune system in germ-free animal models (Calder et al, 2022). The gut microbiome is shaped by multiple factors including age, diet, ethnicity and antimicrobial use, with greater relative shifts in microbial populations occurring after antimicrobial use in the elderly (Saraswati and Sitaraman, 2015; Franceschi et al, 2018). With age, relative increases in pathological proteobacteria alongside concurrent decreases in bifidobacteria are observed. This altered microbiome dysregulates production of key molecules including butyrate, a short-chain-fatty acid (SCFA), which functions as a major source of energy to enterocytes and tissues, maintaining their barrier function while exerting systemic anti-inflammatory and appetite stimulation actions. Therefore, age-related dysbiosis can cause and exacerbate poor nutrition and can attenuate the gut barrier function allowing for bacterial translocation which contributes to antigenic load and systemic inflammation and thus immunosenescence. This further perturbates the ageing individuals' immune system function and increases infection risk (Cristina and Lucia, 2021; Morrison and Preston, 2016).

Nutritional Requirements of the Elderly

Throughout life, the nutritional requirements of the individual change and are altered in the setting of disease. The elderly are at risk of malnutrition due to several coexisting factors, including changes in taste and oral function, cognition, ac-

cess to nutritious food, economic poverty, altered gastrointestinal function, and polypharmacy (e.g., proton-pump-inhibitors (PPI)) (Cristina and Lucia, 2021; Kehoe et al, 2019). This is superimposed onto age-related alterations to carbohydrate metabolism and amino acid synthesis versus younger adults, which are in part due to associated microbiota changes (Badal et al, 2020).

When we consider these overlapping features, it is unsurprising malnutrition in the elderly is a problem. It has previously been estimated that 16% of community elderly patients in the United States consume <1000 calories/day (Evans, 2005). It is because >90% malnourished elderly live in the community that the routine screening of malnutrition in the community by healthcare professionals on general practice registration, admission to care home settings as well as hospital is recommended by the National Institute of Clinical Excellence (NICE) and the British Dietetic Association (BDA, 2017; National Institute for Health and Care Excellence (NICE), 2017; National Institute for Health and Care Excellence (NICE), 2024).

The cost of malnutrition is significant. In 2011–2012, it was estimated that total costs associated with malnutrition to the NHS were £19.6 billion making nutrition a highly attractive cost-saving intervention in a time of increasing austerity. Engaging this could improve functional outcomes in the elderly, reduce infection incidence and attendant mortality particularly in the hospitalised comorbid elderly (BDA, 2017).

The epidemiology of malnutrition is complex and within the elderly is affected by religious and cultural factors. These can affect the perspectives of what constitutes a 'healthy' diet and their design, the accessibility of food by social status and gender, while also influencing acceptable methods of cooking (e.g., frying or boiling) and the serving of food (e.g., raw food) which can increase infection risk (e.g., raw fish and Clonorchis, taeniasis and raw pork). Not only can this lead to malabsorption but also lead to generational malnutrition exacerbated by age (Zhou et al, 2020).

For example, vegan diets as followed by some Hindus and Buddhists may result in vitamin B12, calcium, iron and zinc deficiency, while Islamically prepared chicken can precipitate iron deficiency (Chouraqui et al, 2021). However, it is important to note that due to globalisation, traditional diets are changing. While in Africa historically diets were balanced involving vegetables, grains, and animal proteins ensuring micro/macronutrient balance, with increasing westernisation of food increasing highly refined sugars and animal fats are ingested which are pro-inflammatory and contribute to inflammaging and has led to increasingly negative effects in the elderly age due to being calorically dense and nutritionally deplete (Christ et al, 2019; Oruikor et al, 2023).

Understanding therefore the beliefs and perceptions of diet can help determine the nature of nutritional interventions that are likely to work within a given sociocultural context and thus how best to design and implement them (Livingstone et al, 2023; Monterrosa et al, 2020). This is key within the elderly in whom cultural practices may be more ingrained, and who may have underlying dependency on others for their diet while being inherently more difficult to engage with in public health interventions due to associated social isolation.

Assessing malnutrition in the elderly is complex but necessary to prevent further deterioration and to initiate suitable interventions. The Malnutrition Universal Screening Tool (MUST) is favoured in the UK for all adults due to its reliability and validity when correctly utilised and can determine suitable evidence-based interventions based on the degree of malnutrition recorded. While inconsistent use of the MUST score has been reported within hospitals, issues with its use include the inaccessibility of required information including percentage weight loss in the preceding 6 months and incorrect body mass index (BMI) calculations (Frank et al, 2015; National Institute for Health and Care Excellence (NICE), 2024). In 2019, the Global Leadership Initiative on Malnutrition (GLIM) established a two-tier approach to malnutrition screening to improve the diagnosis and grading of malnourishment by utilising firstly a suitable screening tool, followed by second-tier confirmation by at least one phenotypic (e.g., BMI <20 kg/m^2 or reduced muscle mass etc.) and one aetiological criteria (e.g., diminished intake or inflammation: CRP ≥ 3 mg/L/pre-albumin levels <30 mg/dL) (van Dronkelaar et al, 2023). In those where BMI cannot be used as a phenotypic marker, calf circumference may be used as a sensitive marker of nutrition and sarcopenia in the elderly (Volkert et al, 2019).

While the GLIM criteria have shown promise in acutely unwell elderly patients, it is contingent on sensitive and specific nutritional screens as its first tier with which doubts have been raised in this cohort (Muñoz Fernandez et al, 2021; van Dronkelaar et al, 2023). When evaluated scores such as MUST have a poor sensitivity 40% versus the Short Nutritional Assessment Questionnaire (SNAQ) of 56% in diagnosing malnutrition against the GLIM criteria. Indeed, amongst all utilised screening tools between analysis of those <70 years old and ≥ 70 years old only the Mini-Nutritional Assessment-Short Form (MNA-SF) demonstrated greater sensitivity in those ≥ 70 years at 89% when liberal cut-offs were used but at the risk of overdiagnosis making it useful as an initial screening test (van Dronkelaar et al, 2023; Baek and Heo, 2015). As of 2019, the European Society for Clinical Nutrition and Metabolism (ESPEN) favours the MNA-SF in all geriatric settings as a validated screening tool for malnutrition given its ease and reliability, stating the need to routinely rescreen patients particularly where nutritional interventions are implemented (Volkert et al, 2019). Furthermore, the 2024 ESPEN guidance highlighted the use of the GLIM criteria in the setting of dementia, emphasising the need to integrate such nutritional tools and utilise them routinely as part of the comprehensive geriatric assessment (Volkert et al, 2024).

For healthy ageing adequate nutrition is key, providing maintenance of functional status, cognition and physiological barriers (e.g., epithelia), and may forestall frailty, disease emergence and sarcopenia which progresses with age at typically 3% muscle strength loss/year. However, despite this awareness and the effects of hospitalisation on their respective progression, few nutritional interventions exist for the elderly (Dowling et al, 2024; Kaur et al, 2019). This is a missed opportunity as it is estimated 85% of community elderly patients would show improvement in their chronic disease management, if proper nutrition was instituted, as observed in chronic obstructive pulmonary disease patients and their symptomatology and quality of life (Cristina and Lucia, 2021; Weekes et al, 2009). While the immune

system is not responding to an infection it is highly metabolically active, requiring ~1600 kJ (~400 kCal) daily to function, which can increase by 30–60% in the setting of infection (Straub, 2017). Importantly, different components of the system utilise different metabolic pathways, i.e., neutrophils and M1 macrophages favour glycolysis while naïve T-cells and M2 macrophages predominantly utilise oxidative phosphorylation and fatty acid oxidation. This is attenuated in the setting of active infection (e.g., effector T-cells and aerobic glycolysis), malnutrition and co-existent disease (e.g., diabetes, cancer) and likely further altered by advancing age (Hu et al, 2024). It is for this reason that immunometabolism is considered a promising target for intervention to reverse immunosenescence and improve immunity during coexistent immunosuppression and ageing, although at present remains in its infancy.

While overall energy requirements decrease with age, it is important to recognise that there are relative increases in the requirements of protein (>1 g/kg/day), vitamin D aiming to achieve serum levels of 40–60 nmol/L and calcium which can help maintain physical function and cognition (Dowling et al, 2024; Rolf et al, 2022). As such, it is important to recognise that proper nutrition refers to not only the correct quantity but quality of food, with evidence that Mediterranean diets, rich in fruits, vegetables, olive oil and plants versus meats, can significantly reduce frailty risk in the community elderly (odds-ratio = 0.44; $p < 0.001$) due to their clear antioxidant and immunomodulatory properties (Kojima et al, 2018; Ni Lochlainn et al, 2021). However, such food items are often inaccessible to elderly patients due to their higher cost, with only 32% of elderly adults (65–74 years) consuming the recommended 5 fruits and vegetables/day (Scientific Advisory Committee on Nutrition (SACN), 2021). It is therefore not uncommon that the elderly eat higher than recommended processed foods, which enhance systemic inflammation and with-it frailty and chronic disease development and progression (Ni Lochlainn et al, 2021). It is because of the systemic inflammatory state coupled with dietary imbalance that sarcopenic obesity is seen. While obesity is considered a major problem among the young, where it is often coupled with corresponding increases in muscle mass, within the elderly, obesity, which affects 35% globally, is often associated with sarcopenia where it predicts disability and mortality. This juxtaposition reflects the growing evidence that adipose tissues are not biologically inert but rather through adipokines (e.g., leptin, adiponectin) and cytokine release (e.g., IL-6) can potentiate low-grade inflammation (e.g., oxidative stress) and accelerate progression of multiple disease states as well as existing sarcopenia in the elderly through decreased myocyte proliferation, myocyte differentiation and insulin resistance and may be exacerbated by concurrent suboptimal protein intake (Axelrod et al, 2023). Given the links between sarcopenic obesity and poor prognostic outcomes, ESPEN has detailed diagnostic classification to assist clinicians in this regard (Donini et al, 2022).

Overall, calorie requirements in the elderly while lower than in younger adults due to reductions in basal metabolic rate are estimated at 30 kcal/kg/day. Even in the presence of diabetes, 50–55% of daily calories should be derived from carbohydrates alongside 25–30 g fibre/day to promote gastrointestinal health and function

through its anti-inflammatory action (Volkert et al, 2022). Of macronutrients, protein is highly required with protein-energy-malnutrition key in driving sarcopenia prevalence (>50% at 80 years old), immobility, reduced wound healing and infection risk with protein supplementation aiding to reduce their respective development (Kaur et al, 2019; Milne et al, 2009). As such the elderly require minimally 1 g/kg/day equally spaced throughout the day to maximise muscle protein synthesis with particular enrichment of leucine, and this should rise in acute/chronic illness (1.2–1.5 g/kg/day) and malnutrition (2 g/kg/day) (Kaur et al, 2019; Volkert et al, 2022). Within hospitals, therefore, the need to provide suitable calorific, nutritious, appetising geriatric diets need to be made to not only achieve physiological requirements but also account for baseline deficiencies through appropriate malnutrition diagnosis (e.g., GLIM). As such the nutritional needs of the elderly are complex and difficult to truly capture. By doing so, however, could assist greatly in enhancing recovery from both infectious insults, improve functional recovery and reduce the spiral of descent into worsening malnutrition and infection incidence.

Nutrition and Infection Risk

Where present, malnourishment in the elderly predicts the development of common infections including pneumonia, complications in the postoperative setting and infections in those with cancer. It may also contribute to the high rates of and mortality from bloodstream infections noted in the elderly (Chen et al, 2021; Ibarz et al, 2024; Li et al, 2023a). Additionally, malnutrition often complicates and may predict worsened outcomes in stroke, falls and pressure ulcers which are highly prevalent in this age-group (Leach et al, 2013; Volkert et al, 2019). It is clear therefore that a bidirectional and synergistic relationship between infection and malnutrition exists which is exacerbated by ageing (Esme et al, 2019; Maggini et al, 2018; Marcos et al, 2003; Scrimshaw, 2003) (Fig. 1).

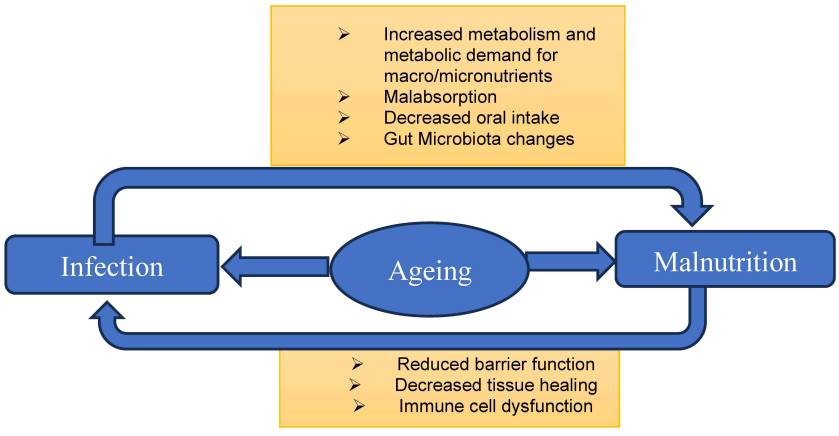

Fig. 1. The reciprocal interaction between malnutrition and infection potentiated by age.

For the immune system to function, it requires energy and is modulated by both macronutrients and micronutrients. Malnutrition is an occult form of immunodeficiency resulting in both qualitative and quantitative deficits within both the

innate and adaptive immune response and alongside associated deregulated glucocorticoid production significantly exacerbate infection risk (Bourke et al, 2016). Infection commonly induces anorexia through microbial products (e.g., lipopolysaccharide) and cytokines (e.g., IL-1β), which act centrally on the hypothalamus alongside peripherally through altered hormone release (e.g., leptin) to suppress appetite and nutrient metabolism. Compounding this is prevalent cultural practices during infection which include withdrawing food to 'starve' the fever (Langhans, 2000; Scrimshaw and SanGiovanni, 1997). Infection in the elderly can produce a severe catabolic state via pro-inflammatory cytokine release (e.g., TNF-α) and insulin resistance which induce skeletal muscle breakdown and lipolysis to sustain energy requirements and to produce immune cell products. Moreover, as highlighted malnutrition can affect the microbiome and thus epithelial integrity including the intestinal mucosa compounding the problem leading to relative malabsorption as well as hyperpermeability to pathogens and secondary infection in the setting of a now dysfunctional and compromised immune system (Cristina and Lucia, 2021; Bourke et al, 2016; Morrison and Preston, 2016). During fever and each 1 °C increase in body temperature, the basal metabolic rate increases by 10–13%. (Scrimshaw and SanGiovanni, 1997). When this happens at a time of diminished intake and increased nutrient demand, it can push elderly patients with infection, who have insufficient bodily reserves, into frank deficiency. This limits the ability of the individual to recover and increase susceptibility to further infection and the development of frailty. The impact of nutrition on reductions in infection incidence has been demonstrated for multiple food-items including with high whey-protein diet (>20 g/day) where it reduced all cause infection in nursing home residents while 300 mL/day black chokeberry juice high in vitamin C significantly reduced elderly associated urinary tract infection and thirdly resolution of lymphopenia which is linked with infection development and hospitalisation, in nursing home residents with zinc supplementation (Psihogios et al, 2022).

The elderly have high levels of critical illness due to immunosenescence and malnutrition often requiring hospitalisation, with infection a leading cause. Where admitted with infection the elderly often present more severely and atypically versus the young (Esme et al, 2019). Given this, it may become necessary in the elderly to perform intravascular or nasogastric insertion for the delivery of therapy. This further compromises barrier function, increasing the risk of secondary infection while the use of broad-spectrum antibiotics can lead to gut microbiome alterations and increased risk of opportunistic infections (e.g., Clostridioides difficile) exacerbating poor nutrition and delirium (Esme et al, 2019; Schoevaerdts et al, 2021). In fact, versus younger adults, the elderly after sepsis and critical illness are more likely to develop a chronic catabolic state despite the resolution of the original infection termed persistent inflammation, immunosuppression and catabolic state (PICS) syndrome. In this state patients can be relatively resistant to high protein supplementation, have high levels of oxidative stress worsening post-infectious immune dysfunction and resulting in high secondary infection risk and a spiral of decline (Mankowski et al, 2022; Chadda and Puthucheary, 2024). This therefore is a key process which needs to be elucidated if we are to change outcomes in this patient

group and which could be reversed through appropriate pharmacological agents and nutrition.

Micronutrients such as vitamins A, C, E, and minerals including zinc and iron are often underrepresented in diets, with 2–5 billion people worldwide deficient in $\geq$1 with the elderly often multi-deficient (Katona and Katona-Apte, 2008; Vural et al, 2020; Passarelli et al, 2024). This is superimposed with the development of comorbidities in ageing which directly affect micronutrient stores and metabolism leading to deficiency, e.g., renal failure and vitamin B1, K, D and zinc deficiency (Berger et al, 2022).

Within geriatric cohorts, several risk factors have been established for risk of micronutrient deficiency including those >85 years old, pre-frail/frail, receipt of polypharmacy, and lack of nutritional supplementation (Conzade et al, 2017). Therefore, there is a need to consider micronutrient ratios when assessing diets and to assess without confounders the effects of nutritional interventions with associated health outcomes. This could also allow us to understand the relative nutritional quality of foods, determine the relative healthiness and balance of a given diet and the nature of deficiencies and how best to manage them (Kelly et al, 2018). For instance, there is evidence of additive action between vitamin A and D supplementation on immune function and synergistic action between vitamin A and zinc on T-cell function with ESPEN highlighting how daily requirements of micronutrients alter according to normal daily dosing, in critical illness and pro-oxidant disease states which the elderly are at risk of (Berger et al, 2022; Gombart et al, 2020).

Due to impracticalities in their measurement including poor estimation of bodily stores via serum concentration, need for specialist equipment (e.g., high-performance liquid chromatography), prohibitive cost, and the uncertainty of defined cut-offs, many micronutrients are often not measured in routine blood tests making true prevalence of micronutrient deficiency in the elderly difficult to ascertain. Moreover, acute phase reactants are well known to affect and decrease serum micronutrient levels including vitamin C, zinc, vitamin A, selenium and iron making their assessment in severe infection challenging to interpret and thus correct (Berger et al, 2023). Importantly, while such micronutrients have multiple homeostatic functions, their deficiency often presents subclinically and globally with overlapping deteriorations in functional status, resilience to infection and cognition (Hoffman, 2017).

Vitamin A, C, E like other micronutrients cannot be synthesised endogenously and while they are recognised to have several important non-immune functions (e.g., vitamin A and vision), they also have diverse and complementary immune functions. These include their antioxidant action; their ability to maintain mucosal surface function and integrity with their deficiency linked with diarrhoeal/respiratory illness and malabsorption and finally their ability to promote function and maturation of innate and adaptive immune cells (Carr and Maggini, 2017; Cheng et al, 2022; Flatby et al, 2023; Huang et al, 2018; Imdad et al, 2022; Lee and Han, 2018; Yu et al, 2023; McAuliffe et al, 2020; Ni et al, 2022; Shankar and Prasad, 1998; Swenson et al, 2018; Tansarli et al, 2013; Thornton et al, 2014; Tourkochristou et al, 2021) (Table 1).

In severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for instance, vitamin D supplementation was utilised with mixed evidence of effect due to trial heterogeneity. Indeed, in one meta-analysis utilised regimens involved bolus's of vitamin D3 up to 200,000 IU with variable dosing thereafter and primary outcomes following either confirmed diagnosis or suspicion of SARS-CoV-2 infection (Rawat et al, 2021). While statistically insignificant reductions in mortality, duration of mechanical ventilation and admission to intensive care unit (ICU) were reported with supplementation this has been recently challenged in a high-quality umbrella meta-analysis with mortality and disease severity being attenuated in those receiving supplementation but with important limitations including optimal dosing remaining (Jamilian et al, 2024; Rawat et al, 2021). Consistently, however, vitamin D deficiency has been linked with increasing incidence of viral infections like SARS-CoV-2 and is predictive of longer duration of hospital stay. Overall recommendations in SARS-CoV-2 are limited by small cohort size, short durations of follow up, unmeasured baseline deficiency and trial heterogeneity but do suggest at the very least that vitamin D deficiency may act as a surrogate marker of viral fitness and subsequent disease within the infected host (Imran et al, 2024).

While evidence exists for micronutrient supplementation to reduce infection incidence in children, the evidence in elderly patients is comparatively weak. A good example of this is the vitamin A supplementation program as advocated by the World Health Organization for children 6–59 months in areas of prevalent vitamin A deficiency, where it reduces all-cause mortality and specifically morbidity and mortality from diarrhoeal disease and measles infection (WHO, 2011; Maggini et al, 2018). This however has been challenged recently with conflicting results from larger randomised trials where a more neutral effect is seen with concerns that supplementation in this manner does not reliably improve serum vitamin A levels highlighting the need instead for sustained dietary change (Bjelakovic et al, 2024). In contrast, in adults, vitamin A supplementation is much less certain with little randomised control trial data demonstrating any protective benefit and instead perhaps harm, but is comparatively less investigated. Where studied, there is some evidence vitamin A in adults may still attenuate viral diseases, including measles complication rates (e.g., diarrhoea) and enhance human papillomavirus (HPV) infection clearance. Compounding this issue is the lack of reliable cut-off for what constitutes deficiency of vitamin A which requires correction (Bjelakovic et al, 2024; Sinopoli et al, 2022).

Like vitamin A, vitamin E is often the subject of study in adults due to its significant role as an antioxidant and is typically found in plant-based food items. While rare to be frankly deficient patients at risk include those individuals with conditions affecting fat absorption (e.g., pancreatitis, cystic fibrosis, Crohn's disease) with supplementation linked to reductions in disease progression in non-alcoholic fatty liver disease (Karunarathna et al, 2024).

Vitamin E has multiple effects of note on the immune system with supplementation at 800 IU/day able to improve *in vivo* T-cell function and at an optimal dose

Table 1. Micronutrient immunomodulatory function and their links with infection.

Micronutrient	Immune function	Infection link
Vitamin A	• Differentiation and function of neutrophils and macrophages • T-cell migration and activation • Ig synthesis • Mucosal regeneration	• Gastrointestinal and respiratory infection • Measles mortality and morbidity
Vitamin E	• Antioxidant • Cell membrane integrity • Increased NK cell activity • T-cell activation and Th1/2 Differentiation	• Respiratory infection
Vitamin C	• Antioxidant • Neutrophil migration and function (ROS formation, chemotaxis) • Vitamin E regeneration • B and T-cells proliferation and differentiation • Collagen synthesis	• Wound healing • Respiratory infection
Copper	• Ig synthesis • Cytotoxic T-cell function • Thymic gland structure • Neutrophil ROS formation	• Overall increased infection risk in cirrhosis • Gastrointestinal infection
Iron	• Neutrophil and NK cell function • Macrophage polarization • Cytotoxic lymphocyte differentiation • Antibody responses	• Bloodstream infection • Respiratory infection • Post-operative infection
Zinc	• Neutrophil and NK development and function • Macrophage phagocytosis • Thymic gland function • Antibody synthesis • Antioxidant	• Respiratory infection • Sepsis • Wound healing

Ig, immunoglobulin; NK, natural killer cell; ROS, reactive oxygen species.

of 200 IU/day able to improve vaccine response rates with evidence of greater efficacy in elderly patients versus younger adults (Meydani et al, 2018; Lewis et al, 2019). Multiple studies have also highlighted reduced re-hospitalisation rates from pneumonia alongside lower incidence and shorter duration of respiratory illness in those utilising vitamin E supplementation of 200 IU/day. Moreover, in the elderly reduced mortality and safety have been demonstrated at this dose. The response however is not consistent with other studies noting no observable effect. However, multiple factors are thought to explain this including smoking status, baseline deficiency and polymorphisms in vitamin E-associated apolipoproteins. It is suggested much like in vitamin A whether an increased recommended daily allowance of vitamin E should be pursued given these potential benefits within the elderly and changes with age in vitamin E metabolism (Meydani et al, 2018; Lewis et al, 2019).

Notably, micronutrients are enriched in only certain food types and have limited bodily reserves meaning they are required throughout life (Carr and Maggini, 2017; Berger et al, 2022). This is key as they are not often present in the food accessible to elderly patients and particularly in those hospitalised or in healthcare facilities. More importantly, even where nutritious foods are chosen, the improper preparation and cooking of them can destroy or purge nutrients and includes practices such as peeling, drying, blanching and overboiling vegetables, improper storage (optimal 15–18 °C) or competitive inhibition by other components of the diet (e.g., phytate and iron) and concurrent medications (Henry and Massey, 2006; Berger et al, 2022). Therefore, it is important to not only design varied diets for the elderly which contain adequate micronutrients but also prepare them in a way that minimises micronutrient attrition while retaining texture and taste, which are affected by age. To achieve this, robust research into micronutrient metabolism in the elderly in both health and disease, alongside large population data to assess baseline deficiency prevalence, will be required. While the routine use of multivitamins in this age group, therefore, may provide benefits through reliable intake, this must be balanced by the risks which include toxicity as seen with long-term vitamin E supplementation and the historic concern regarding the development of heart failure particularly in those with recent myocardial infarction, although this has been since disproved albeit in younger healthy women (Chae et al, 2012).

Of typically measured and replaced micronutrients in the elderly, vitamin D is one of the most prominent. Vitamin D is primarily obtained by UV-light exposure, and in the elderly who may have immobility and social isolation, their exposure to UV-light is significantly reduced. Moreover, due to age-related declines in the ability of elderly individuals' skin to synthesise precursor vitamin D from UV-light (~40% that of the young) as well as high rates of co-existent liver and kidney disease, production of active vitamin D is severely diminished. Within the diet, natural sources of vitamin D are poor, often achieving 150 IU/day versus the recommended intake of 200–800 IU/day, meaning supplementation is the only feasible method to achieve the required daily intake (Giustina et al, 2023; Lin et al, 2021).The role of vitamin D in reducing osteoporosis, falls and sarcopenia are important functions in the elderly (Arik and Ulger, 2016). Vitamin D does however have immune functions, as there is diverse expression of the vitamin D receptor in epithelial cells,

neutrophils and macrophages helping to regulate interferon-γ synthesis, toll-like-receptor expression, cathelicidin synthesis and antiviral-immunity with epidemiological evidence of vitamin D deficiency and viral respiratory tract infection and intracellular bacterial infection (e.g., Tuberculosis) incidence (Ismailova and White, 2022; McAuliffe et al, 2020). While data is conflicting, there is evidence that suggests that vitamin D supplementation can reduce acute respiratory infections, with greater effect in those who are very deficient (<25 nmol/L, 25-hydroxyvitamin D levels) (adjusted-odds-ratio 0.30) (Martineau et al, 2019). While the D-health trial a large (n = 21,315) double-blind placebo-controlled trial studying monthly high-dose vitamin D (60,000 IU) in healthy replete 60–84-year-olds did not demonstrate a reduction in hospitalisation due to respiratory infections, it did demonstrate the safety of this approach and that supplementation could however reduce the duration of hospitalisation and possibly attenuate respiratory infection severity as highlighted by previous analysis of D-health data, which is of potential benefit to the elderly population and those in healthcare facilities (Pham et al, 2023).

Zinc supplementation is common in children as an evidence-based treatment for treatment and resolution of diarrhoea and prevention of relapse (Khan and Sellen, 2011). Zinc is amongst the most prevalent micronutrient deficiency in otherwise healthy elderly adults secondary to reduced gastrointestinal tract absorption, poor diet and micronutrient: drug interactions (Chandra, 2002; Mocchegiani et al, 2013). Zinc importance stems from several reasons; firstly, it is important in mediating the utilisation of vitamin A and modulating the requirement of vitamin E. Secondly, zinc is essential in cellular proliferation and signal transduction, which immune cells utilise to function (Kaur et al, 2019). Finally, zinc deficiency as highlighted helps drive immunosenescence as it is linked with accelerated thymic atrophy and both innate and adaptive immune cell dysfunction (Maywald et al, 2017). In the elderly, zinc supplementation in 50 healthy elderly (55–87 years) with no chronic diseases demonstrated reductions in the overall incidence of infection versus placebo ($p < 0.001$) over a 12-month period with reductions in markers of oxidative stress (e.g., malondialdehyde and 4-hydroxyalkenals) ($p = 0.0002$) suggesting it can modify inflammaging and related immunosenescence (Prasad et al, 2007). Zinc has been investigated extensively in respiratory tract infections due to its important function in antiviral immunity with normal levels linked with reduced pneumonia risk in observational studies (Meydani et al, 2007). In mice, a similar observation has been described with zinc deficiency potentiating *Acinetobacter baumannii* respiratory infection and its subsequent dissemination in an IL-13-dependent manner. This is important given *Acinetobacter baumani* is an increasing and emerging multi-resistant pathogen which leads to mortality, particularly in nosocomial infections in those critically unwell and the elderly (Palmer et al, 2024).

Zinc supplementation and repletion alone or in combination with other micronutrients have in the elderly been linked with reductions in the number of respiratory infections, all infections and greater vaccine humoral response rates even at low dosages (20 mg/day) (Barnett et al, 2010). This has corresponded in those supplemented who achieved normal serum zinc levels ($\geq$70 µg/dL) with significant decreases in the duration of pneumonia and antibiotic days which is significant in

this age group ($p \leq 0.004$) given the increasing rates of antimicrobial resistance observed in the elderly and the risks of transmission in healthcare facilities (Meydani et al, 2007). Finally, a 2021 systematic review studying the effects of zinc supplementation on viral respiratory tract infection demonstrated that oral/topical (nasal) zinc was linked with reductions in symptom duration and risk of developing mild to moderately severe symptoms compatible with influenza-like illness over a wide range of doses making this an important area of further work as included studies were limited by small study size and trial bias (Hunter et al, 2021).

The elderly are at risk of pressure ulcers due to alterations to the vascular supply to the skin, relative immobility and reductions in healing. The significance of pressure ulcers cannot be understated with up to a third of hospitalised elderly patients developing pressure ulcers with an associated cost of between £1214–£14,108 based on severity per case and £3.8 million/day for the NHS which would improve with proper nutrition and hydration (Dealey et al, 2012; Wood et al, 2019). Zinc assists in tissue epithelisation and granulation supporting tissue healing. While zinc supplementation has not shown efficacy in healing arterial and venous ulcers, within pressure ulcers (category 1–4) significantly enhanced healing rates (relative risk 1.44; $p = 0.043$) in geriatric patients has been noted when given oral or topically versus control (Wilkinson, 2014; Song et al, 2020). Given the requirement for protein also in wound healing the European Pressure Ulcer Advisory Panel et al (2019) suggests that individuals with category 2 or higher ulcers who are or at risk of being malnourished should receive high protein, high-calorie diets supplemented by zinc and oral supplements. This makes zinc an important supplement which could vastly improve outcomes in the elderly and should be routinely considered in high-risk individuals.

While micronutrient supplementation has biological plausibility and is performed in certain populations (e.g., folate supplementation and pregnant mothers), there are several issues of note within the elderly including access, cost, dosing, comorbidities and prescribed medications which may alter micronutrient metabolism and absorption. For instance, micronutrient supplements may interact with each other in a deleterious manner (e.g., iron-reducing zinc absorption); interact with common medications (e.g., PPIs and reduced vitamin B12 absorption); increase micronutrient excretion (e.g., Diuretic and Thiamine); inhibit micronutrient activity (e.g., isoniazid and vitamin B6) or reduce medication efficacy (e.g., vitamin E and coumadin) (Marra and Bailey, 2018; Berger et al, 2022). Therefore, while a population issue, individualised targeted actions are required based on sex, age, medications, baseline deficiency and severity of illness.

This requires accurate identification of at-risk elderly individuals, estimation of macronutrient demand and use of appropriate markers of micronutrients to estimate correctly underlying deficiency and allow for the correct prescription of supportive nutrition with regular re-assessment.

By detailed epidemiological assessment of malnutrition in the elderly according to socioeconomic status and sociocultural factors, economic assessment and feasibility data could be obtained for the design of a targeted nutrition program for the elderly in both the community and hospital.

It is clear therefore that the role of nutrition in the elderly needs to be considered as part of a multimodal approach to maintaining cognitive and physical health given the evolving epidemiology of ageing. As highlighted, malnutrition is a polyfactorial problem modulated by many factors, including socioeconomic factors, which require attention if wanting to achieve long-term improvements in geriatric health. As such, it is important to ensure education of nutrition to the elderly and their caregivers, which is poor and mirrors public underappreciation of what constitutes good nutrition, without which, progression of chronic disease, reductions in resilience to infection and exacerbation of pre-existing malnutrition will occur.

How Should We Minimise the Problem?

It is clear that awareness of nutrition by clinicians is poor, including its effects on chronic disease management and prevention. Education however on nutrition is poor at the undergraduate level with most UK medical students receiving an average of 26.9 hours in nutrition education with great variation therein (Yoon et al, 2022).

This is something which requires immediate attention given the increasing demands the elderly offer to the NHS and the cost-saving that this could afford. While the Association for Nutrition (2021) has developed a curriculum for medical schools in 2021, this will not assist in modifying practice on the front line where care is taking place. This is particularly important given that discrepancies in nutrition learning objectives within postgraduate curriculums are noted between surgical and medical doctors, with many doctors feeling unable to educate or advise patients on this important topic (Ganis and Christides, 2021). As such, the need for targeted postgraduate teaching on how malnutrition can affect disease progression and outcomes in the elderly and encouraging routine review of nutrition and nutritional status including micronutrient status by utilising suitable screening methods (e.g., GLIM) and integrating this into admission clerking could lead to significant improvements. Indeed, international research collaborations like the Malnutrition in the Elderly (MaNuEL) program (2016–2018) which helped define and expand knowledge of malnutrition in the elderly and integrate the education and screening of malnutrition alongside interventions and management, demonstrates how we can effectively perform malnutrition research in the elderly and improve outcomes in the UK (Corish and Bardon, 2019).

Conclusion

The nutritional needs of the elderly are unique with total-calorie, protein and micronutrient deficiency common in both community and healthcare settings. The effect of this includes increases in sarcopenia, immobility, malabsorption and altered immune system function culminating in increased risk of infection. This unfortunately leads to a self-fulfilling prophecy of worsening infection and malnutrition risk from which the patient may not recover. While protein, vitamin D and zinc deficiency increase infection risk, it appears those with overt deficiency likely benefit the most from supplementation, with optimal dosing likely dependent on, e.g., age, comorbidity, weight, presentation and degree of pre-existing deficiency.

It is clear however that there is a real need to accurately establish the level of nutritional deficiency at the population and individual level and improve malnutrition diagnosis within this population, which currently is poor and complicated. This will require an assessment of elderly populations in different settings, i.e., community versus healthcare facilities, and among those of different ethnicities and diets, as well as comorbidities that may also modulate nutrition and immunological function. While micronutrient supplementation offers obvious benefits, the optimal dosing of these based with long-term safety data is required, which is currently lacking. Therefore, a well-designed randomised control data is required requiring investment and collaboration between centres.

Through the design of suitable geriatric foods, which are calorific, nutritious and appealing, the effects of inmmunosenescence may be dampened, helping to promote immune system function, response to vaccines and reduce age-related infection risk.

Key Points

- Aging is a complex social, cultural and physiological process typified by changes to the immune system, namely immunosenescence, and alterations to nutritional status, culminating in increasing incidence, morbidity, and mortality from infection.
- Malnutrition in the elderly is common, underdiagnosed and multifactorial in nature. Often presenting in a myriad of ways including deterioration of chronic disease management, reduced mobility, frailty, infection and delayed recovery from clinical illness.
- Screening of malnutrition in the elderly is poor with the GLIM criteria involving a two-tier approach (screening tool and phenotypic/aetiological criteria) the most optimal method. The MNA-SF screening tool offers increased sensitivity in the elderly versus the traditional MUST score.
- Micronutrients (e.g., zinc) are amongst the most common nutrient deficiencies affecting the elderly and exacerbate age-related immune dysfunction. Promising micronutrients to preserve immune function include zinc, vitamin E and vitamin D.
- Infection increases basal metabolism and increases macronutrient and importantly micronutrient demand leading to risks of overt deficiency which can lower the threshold to subsequent infection. Therefore, nutritional supplementation must factor in the baseline deficiency, severity of underlying illness and patient comorbidities.
- Targeted nutritional interventions in the elderly can help restore immune cell function and reduce infection risk, however the dose to do this needs to be defined and must be balanced with the risks of toxicity.
- Education of patients and healthcare professionals regarding nutrition is necessary to improve health outcomes in the elderly in a cost-effective manner.

Availability of Data and Materials

All data included in this study are available upon request by contact with the corresponding author.

Author Contributions

DAW was the sole author and was responsible for the design of the work, drafting and revision of content, and approval of the version to be published. DAW has participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The author declares no conflict of interest.

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