**Title:** Nutrition and Immunity: Perspectives on Key Issues and Next Steps

**Author List:** Carolyn L. Dunbar, Harold M. Aukema, Philip C. Calder, Deanna L. Gibson, Sarah E. Henrickson, Saad Khan, Geneviève Mailhot, Shirin Panahi, Fred K. Tabung, Mei Tom, Julia E. M. Upton, Daniel A. Winer and Catherine J. Field

**Affiliations:**

**CL Dunbar:** Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, Alberta, Canada

**HM Aukema:** Department of Food and Human Nutritional Sciences, University of Manitoba, Winnipeg, Manitoba, Canada

**PC Calder:** School of Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, United Kingdom; NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, United Kingdom

**DL Gibson:** Department of Biology, Faculty of Science, Okanagan Campus, The University of British Columbia**,** Kelowna, British Columbia, Canada

**SE Henrickson:** Division of Allergy Immunology, Department of Pediatrics, The Children’s Hospital of Philadelphia, Philadelphia, PA, USA; Department of Microbiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; USA

**S Khan:** Division of Cellular & Molecular Biology, Diabetes Research Group, Toronto General Research Institute (TGHRI), University Health Network, Toronto, Ontario, Canada; Department of Immunology, University of Toronto, Toronto, Ontario, Canada

**G Mailhot:** CHU Sainte-Justine Research Center, Montreal, Quebec, Canada; Department of Nutrition, Faculty of Medicine, Université de Montréal, Montreal, Quebec, Canada

**S Panahi:** Department of Physical Education, Université Laval, Quebec City, Quebec, Canada and Canadian Nutrition Society, Ottawa, Ontario, Canada

**FK Tabung:** Department of Internal Medicine, Division of Medical Oncology, College of Medicine and Comprehensive Cancer Center**,** The Ohio State University, Columbus, OH, USA

**M Tom:** Nutrition Service, Alberta Health Services, Edmonton, Alberta, Canada

**JEM Upton:** Department of Pediatrics, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; Division of Immunology and Allergy, Department of Pediatrics, SickKids Food Allergy and Anaphylaxis Program, Hospital for Sick Children, Toronto, Ontario, Canada

**DA Winer:** Buck Institute for Research on Aging, Novato, CA, USA; Leonard Davis School of Gerontology, University of Southern California, Los Angeles, CA, USA; Division of Cellular & Molecular Biology, Diabetes Research Group, Toronto General Research Institute (TGHRI), University Health Network, Toronto, Ontario, Canada; Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada; Department of Immunology, University of Toronto, Toronto, Ontario, Canada

**CJ Field:** Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, Alberta, Canada

**Corresponding author:** Catherine J. Field (Catherine.field@ualberta.ca)**Abstract**

In January 2022 a group of experts came together to discuss current perspectives and future directions in nutritional immunology as part of a symposium organized by the Canadian Nutrition Society. Objectives included (1) creating an understanding of the complex interplay between diet and the immune system from infants through to older adults; (2) illustrating the role of micronutrients that are vital to the immune system; (3) learning about current research comparing the impact of various dietary patterns and novel approaches to reduce inflammation, autoimmune conditions, allergies, and infections; and (4) discussing select dietary recommendations aimed at improving disease specific immune function. The aims of this review are to summarize the symposium and to identify key areas of research that require additional exploration to better understand the dynamic relationship between nutrition and immune function.

**Keywords:** COVID-19, Immunity, Infection, Inflammation, Aging, Vitamin D, Immunotolerance, Oral Immunotherapy, Food allergy, Dietary patterns, Oxylipins

**Abbreviations**

|  |  |
| --- | --- |
| **BMI** | Body mass index |
| **IL** | Interleukin |
| **NAD** | Nicotinamide adenine dinucleotide |
| **mTOR** | Mammalian target of rapamycin |
| **TNF** | Tumor necrosis factor |
| **AMPK** | AMP-activated protein kinase |
| **VDR** | Vitamin D receptor |
| **RCT** | Randomized controlled trial |
| **25OHD** | 25-hydroxyvitamin D |
| **1,25(OH)2D** | 1,25-dihydroxyvitamin D |
| **COPD** | Chronic obstructive pulmonary disease |
| **PD-1** | Program cell death 1 |
| **Th** | T helper |
| **TSLP** | Thymic stromal lymphopoietin |
| **OA** | Obese asthma |
| **mtROS** | Mitochondrial reactive oxygen species |
| **OIT** | Oral immunotherapy |
| **IBD** | Inflammatory bowel disease |
| **EDIP** | Empirical dietary inflammatory pattern |
| **DII** | Dietary inflammatory index |
| **UC** | Ulcerative colitis |
| **MDP** | Mediterranean diet pattern |
| **WDP** | Western diet pattern |
| **PUFA** | Polyunsaturated fatty acid |
| **AA** | Arachidonic acid |
| **HPLC/MS** | High-performance liquid chromatography mass spectrometry |
| **SPM** | Specialized pro-resolving mediator |
| **LA** | Linoleic acid |
| **ALA** | Alpha-linolenic acid |

**Introduction**

Through the lifespan, the human immune system evolves from an immature system at birth, to an advanced mature network in adulthood that inevitably declines in older age (Simon et al. 2015). The immune system works to protect each individual from harmful foreign antigens by eliminating these potential threats. Components of this intricate system circulate throughout the body, including patrolling lymph nodes, the spleen and gut wall (e.g., Peyer Patches). There are two main components of the immune system: the innate and the adaptive. Together, they protect the organism by responding to factors perceived as dangerous, such as non-self entities including pathogens, toxins, and allergens as well as altered self entities such as cancer cells. Innate immunity includes physical and chemical barriers (e.g., epithelial cells and stomach acid) along with specific cell types that include granulocytes, monocytes and innate lymphoid cells. This form of immunity provides a rapid, nonspecific response initiated through activation of pattern recognition receptors, acting to defend the host and communicate with the adaptive immune system (Marshall et al. 2018; Molnar and Gair 2015; Simon et al. 2015). Inflammation is part of innate immunity and acts to create a hostile environment to pathogens, though it can also play a role in bystander damage to the host. Physiologically this system must be self-regulating and thus resolution of inflammation is an important part of the immune response. Low grade inflammation can be an outcome of incomplete resolution and is defined as chronic systemic elevation of proinflammatory mediators (like C-reactive protein, IL-6, TNF-α along with other immune factors), although a defined threshold or grouping of immune biomarkers has yet to be determined (Calder et al. 2011). Antigen presentation through specific antigen presenting cells (such as dendritic cells) links innate immunity to adaptive immunity. Adaptive immunity includes T and B cells that utilize antigen specific cell-mediated and humoral responses to eliminate pathogens; these include cytolytic cells, such as cytotoxic T cells, as well as antibody production by matured B cells, specifically plasma cells. With regards to tempo, the adaptive immune response is a comparatively slower response than innate immunity, usually taking more than a week to mount a primary response. Finally, the adaptive immune response generates immunological memory, so that re-exposure to a pathogen results in a faster and stronger immune response (Marshall et al. 2018; Mitra et al. 2022; Molnar and Gair 2015; Pecora et al. 2020; Simon et al. 2015). Vaccinations can produce class-switched high-affinity antibodies (e.g. IgG) and are successful due to the induction of immunological memory, priming the system to respond quickly should the host encounter the pathogen. Factors such as low grade inflammation, undernutrition, frailty and obesity influence vaccine efficacy and therefore influence overall herd immunity in various populations (Calder 2021).

The immune system has evolved to appropriately discriminate between harmful and harmless antigens. However, in food allergy, individuals have lost immune tolerance to a specific food antigen (e.g., specific proteins in cow’s milk, eggs, peanuts, shellfish, soybeans). This means that individuals mount an adverse immune response when exposed to the food. Although food avoidance is typically prescribed, more recently oral immunotherapy (OIT) approaches have been developed to incorporate small incrementing amounts of known food antigens to ultimately mitigate the adverse immune response, with the hope of developing a higher threshold of tolerance (De Martinis et al. 2020; Yu et al. 2016).

Immune function can be influenced by the gut microbiota, with colonization during infancy, diversifying and stabilizing in early childhood then declining in older age (Mills et al. 2019). The microbiota provides a physical barrier for protection in addition to interacting with gut-associated lymphoid tissue and intestinal epithelial cells to modulate immune function directly, for example through cell-to-cell contact, or indirectly through bioactive components, such as short chain fatty acids. Diet is a major predictor of the type of microbes mammals harbor starting in infancy. Poor diet quality can change the microbe-host dynamic resulting in loss of the symbiotic relationship, correlating with increased unregulated and dysfunctional inflammation along with risk of infection and chronic immune-mediated diseases, like inflammatory bowel disease (IBD) and colon cancer (Divella et al. 2021; Gomaa 2020; Mills et al. 2019).

Nutrition is recognized to be a major factor that influences the immune response, with different nutrients, foods and dietary patterns and different body compositions all having an impact (Mitra et al. 2022; Pecora et al. 2020). Diets containing suboptimal concentrations of essential nutrients, (e.g., vitamins, minerals and fatty acids) can impair the immune response and promote oxidative and inflammatory stress. However, the interaction between nutrition, immunity and infection is complex and it is possible that due to effects on metabolism, nutrient deficiencies are a consequence of activation of the immune response (Mitra et al. 2022; Pecora et al. 2020). Vitamin D is a much-studied micronutrient that has an immunomodulatory role (Prietl et al. 2013). It has been widely reported that serum vitamin D concentrations are inversely correlated with autoimmune disease, influenza risk and COVID-19 severity, although further clarification is needed (Ao et al. 2021). Within the aging population it has been observed that micronutrient deficiencies are common. This age group generally has reduced ability to respond to immune challenges in addition to having decreased numbers of some immune cells in the bloodstream leading to higher risk of infection (Maggini et al. 2018). While it is important to consider the quality of the diet in terms of its nutrient composition, the collective effects of a dietary pattern may be more relevant than a single nutrient or single food, as dietary patterns can impact inflammatory status which could modulate non-communicable and infectious disease risk. Dietary patterns that have high inclusion of foods such as fruits, vegetables, berries, and oily fish while being low in soft drinks, refined sweetened foods, salty snacks, and processed meat, are considered health promoting (Cena and Calder 2020). This manuscript will provide a non-extensive overview of the advances in nutrition and immune function from the Canadian Nutrition Society Thematic conference held in 2022. Presenters from this symposium have described recent developments and as experts in their field of research, they have also identified select areas of interest that require further exploration.

**Aging and Chronic Inflammation[[1]](#footnote-2)**

Nutrition and energy related metabolism, as well as nutrient related hormones, contribute to intrinsic immune cell defects with age. For instance, T cells, B cells and macrophages from the elderly have displayed defects in mitochondrial metabolism, which perpetuates an inflammatory phenotype within them, suggesting a key hallmark of inflammaging (Desdin-Mico et al. 2020; Kurupati et al. 2019; Yarbro et al. 2020). Emerging evidence suggests that increased nicotinamide adenine dinucleotide (NAD) degradation by macrophages supports pro-inflammatory activity and a systemic decline in NAD levels is observed with age (Covarrubias et al. 2020). Metabolic hormone signaling, such as growth hormone receptor signaling, can support an increase in the abundance of pathogenic age-associated B cells (Camell et al. 2019). Similarly, insulin receptor signaling in regulatory and effector T cells appears to be crucial for dictating their inflammatory potential (Tsai et al. 2018) or their functional changes with age, which is linked to hyperinsulinemia (Wu et al. 2020).

Signals from the environment can also promote immune cell dysfunction. One such trigger is the gut microbiota, which changes with age. There is also increased gut permeability with aging, resulting in increased inflammatory skewing of immune cells including macrophages, monocytes, B cells and T cells (Bodogai et al. 2018; Khan et al. 2020; Thevaranjan et al. 2017). Age-associated increases in cellular senescence and the senescence-associated secretory phenotype have also been linked with inflammaging. Mice lacking perforin that are unable to clear senescent cells display exacerbated immune cell infiltration across various tissues with age, which can be prevented with senolytics, compounds that remove senescent cells (Ovadya et al. 2018). Similarly, apoptotic debris has been shown to influence the formation of pathogenic age-associated B cells via toll-like receptor 7/9 signaling which further perpetuates inflammaging (Cancro 2020). Finally, aging can be associated with alterations to the cellular sources of immune cell sustaining cytokines, such as adipose tissue interleukin (IL)-33 which may drive a reduction in tolerogenic and pro-thermogenic innate lymphoid cells (ILC)2s with age (Goldberg et al. 2021). Better understanding the causes of inflammaging is especially timely, given the COVID-19 pandemic and the vulnerability of the elderly population (Bartleson et al. 2021).

While aging results in alterations to the immune system, it is unclear which biomarkers can be correlated with longevity and frailty in older adults. Multi-omic longitudinal analyses revealed that immune cells formed an aging trajectory which reflects a continuum of changes in cellular composition over the human lifespan, which could associate with all-cause mortality (Alpert et al. 2019). Recent work has applied artificial intelligence methods to human blood to generate a metric for age-related chronic inflammation (iAge) (Sayed et al. 2021). iAge was correlated with multiple morbidities, immunosenescence, and frailty in humans. Accordingly, centenarians displayed lower iAge index scores. Analysis of factors contributing to iAge revealed potential biomarkers associated with inflammaging, where CXCL9 (a chemokine induced by the pro-inflammatory cytokine IFN-γ), was the most positive contributor to iAge (Sayed et al. 2021). It remains to be determined whether targeting CXCL9 can prevent age-related chronic disease and extend lifespan.

There have been interventions targeted to reduce chronic inflammation with age and enhance the healthspan across mammals. A recent clinical trial evaluated the effects of 14% caloric restriction in humans over a 2-year period, finding that individuals within the treatment group displayed improvements in thymic output and increased pathways associated with mitochondrial biogenesis and anti-inflammatory activity in the adipose tissue (Spadaro et al. 2022). These effects were attributed to the inhibition of the Pla2g7 gene, leading to control of metabolic inflammation (Spadaro et al. 2022). In separate studies, decreasing caloric intake enhanced type 2 immune responses which supports thermogenesis and glucose uptake (Fabbiano et al. 2016). Pharmacological inhibition of the mammalian target of rapamycin (mTOR), a key nutrient sensing molecule, may be a promising target for rejuvenation of the immune compartment; treatment with an mTOR inhibitor, RAD001, increased response to influenza vaccinations in the elderly while decreasing the abundance of pro-inflammaging PD1+ T cells (Mannick et al. 2014). Similarly, mice treated with rapamycin display reductions in senescent T cells as well as a decrease in pro-inflammatory cytokines CCL2 and TNF (Yousefzadeh et al. 2021). Consistently, metformin, an AMPK activator (and also interferes with metabolism (Yerevanian and Soukas 2019)), has been shown to attenuate hallmarks of aging, such as altered nutrient sensing, mitochondrial dysfunction, senescence, and inflammaging (Kulkarni et al. 2020). However, how metformin influences specific immune cell populations in the context of aging remains to be properly evaluated.

**Immunometabolic status in obesity and obese asthma[[2]](#footnote-3)**

To understand the immune dysregulation that takes place in chronic inflammatory disease (or any disease), it is necessary to quantify the cellular and humoral parameters of the healthy immune response and compare them to that system in patients with the disease in question. Assessing immune dysregulation in obesity includes assessment of cell subset frequency, activation state and functional capacity. There has been ongoing progress in the first, including recent evaluation of immune cell populations in obese adult human and mouse adipose tissue using single cell transcriptomics (Emont et al. 2022). It is also important to define key immune signaling pathways altered in affected participants, and potential strategies to retune those key pathways if they impair immune function. For example, it was recently shown that people living with obesity and melanoma have elevated levels of an inhibitory receptor, programmed cell death 1 (PD-1), and enhanced anti-tumor clinical response to anti-PD-1 therapy (Wang et al. 2019). However, while the impact of obesity on broader patterns of immune dysregulation in CD8 T cells remains to be fully clarified, studies of the impacts of perturbations on immune function in the setting of obesity have been instructive. There is increasing evidence of immunometabolic dysregulation in obesity, in part based in part on impaired CD8 T cell cytokine secretion being improved with inhibition of PD-1 ligand 1 (Eljaafari et al. 2021). Laparoscopic sleeve gastrectomy, and subsequent weight loss, has also recently been shown to improve inflammation and metabolic function in patients with obesity (Lo et al. 2022). Inflammatory cytokine signaling (like IL-12, IL-15 and IL-18), consistent with that found in obesity, has also been shown to yield increased expression of TOX, a factor that has effects on transcription and epigenetic state and in mouse cells is necessary for T cell exhaustion (Maurice et al. 2021). Turning from CD8 T cells to consider the impact of obesity on CD4 T cells, there is evidence of impact of diet on T cell differentiation and function, including impacts of individual metabolites; for example, acetate has been shown to increase Th17 differentiation (Park et al. 2015). While mouse models of atopic dermatitis are classically T helper (Th) 2 skewed but obese animals had skewing towards Th17. Treatment with peroxisome proliferator-activated receptor-ƴ (PPARƴ) agonists reduced Th17 responses, making obese mice susceptible to anti-type 2 therapies (Bapat et al. 2022). Finally, with regards to serum factors that are implicated in the altered immunometabolic state in obesity, thymic stromal lymphopoietin (TSLP) is a cytokine associated with type 2 immunity in obese mice; TSLP can cause weight loss secondary to hypersecretion of sebum (Choa et al. 2021).

There is additional complexity at the interface of two of the most common chronic inflammatory diseases, obesity and asthma (Hay and Henrickson 2021). Compared to individuals with obesity or asthma, cumulative effects of obesity and asthma have been observed to amplify proinflammatory factors and alterations to microbiota composition (Michalovich et al. 2019). Many therapies focus on asthmatics who have type 2 immunity and historically obese asthma (OA) has been studied as a non-type 2 immune process. Evaluation of CD4 T cells in pediatric OA has generally focused on amplification of type 1 immunity, with fascinating results, including recent studies evaluating the roles of Rho-GTPase pathways (Rastogi et al. 2020) and examining on the connections among anthropometrics, serum metabolites, hormones, transcriptional and methylation analyses (Thompson et al. 2022). However, it has become clear that OA, like asthma, may be an umbrella diagnosis and that there can be variability in immune phenotypes, including the relative balance of type 1, type 2 and type 17 immunity. The presence of type 2 immunity in this setting may in part be linked to age of asthma onset. Focusing on CD8 T cells in OA, it has been shown, by studying transcriptional data from sputum cells from patients with asthma, there was evidence of altered CD8 T cell activation state, as observed in obesity, which remains to be further clarified (Peters et al. 2019). Most recently, patients with OA were found to have lower levels of paraoxanase 2 (PON2) in bronchial epithelial cells, which can mitigate the impacts of mtROS, and may make those cells more susceptible to oxidative stress (Winnica et al. 2022). Chronic inflammatory diseases, like OA, dysregulate the immunometabolic function in T cells, likely altering patients’ ability to combat the upper respiratory viruses that trigger asthma exacerbations. Continued investigation of the immunometabolic impacts of obesity and asthma, with a focus on targetable mechanisms, must remain a key focus of the field.

**How to induce immunotolerance: Lessons from food allergen immunotherapy[[3]](#footnote-4)**

Until recently, food allergy was almost entirely managed by avoidance of the culprit food and preparation for emergencies by carrying an epinephrine autoinjector. However, there are highly effective food allergy prevention and treatment strategies focused on food. These approaches require focus on appropriate care through the ages. Early introduction and dietary incorporation of highly allergenic foods is a powerful example of the induction of immune tolerance. In a pivotal study, 4-11 month old infants at high risk of developing peanut allergy who avoided peanut until age 5 years old were more likely to have a peanut allergy than those infants who were randomized to have peanut deliberately and consistently included in their diet (Du Toit et al. 2015). These and other studies have led to the recommendation that allergy to peanut, egg, and likely other foods can be prevented through early introduction (at around 6 months) and consistent dietary exposure, as was recently summarized (Abrams et al. 2021).

Once a food allergy is established, it can be managed in some patients with a food-based approach referred to as oral immunotherapy (OIT). Food allergen immunotherapy aims to downregulate the immune response from a dominant T Helper 2 and IgE hypersensitivity reaction via upregulating a T Helper 1 and T regulatory response, promoting desensitization (van Zelm et al. 2019). In OIT, the individual with food allergy eats the food to which they are allergic, starting with tiny doses and increasing over time in a medically supervised process. OIT desensitizes the food allergic individual, meaning it increases the amount of the culprit food that can be safely ingested before an allergic reaction occurs (Begin et al. 2020; de Silva et al. 2022). Increasing the threshold at which an allergic reaction occurs is beneficial, as this increased threshold should reduce the risk of an allergic reaction from accidental exposure (Eiwegger et al. 2019). Interestingly, OIT does not appear to induce durable oral tolerance in most children and adults who embark on the process (de Silva et al. 2022). Most individuals remain food allergic and are in a desensitized state, where the increased threshold to a food allergen can be reduced for various reasons including no longer ingesting the food routinely, or during physiological stressors such as exercise or illness.

OIT in the first few years of life may have a different efficacy than in later years. In the IMPACT study (Jones et al. 2022), children with peanut allergy aged 12 months to younger than 48 months were provided either placebo or peanut OIT (dosing up to ~8 peanuts/day) for 2.5 years. Subsequently, the children avoided peanut for 26 weeks and were assessed to determine if they experienced an allergic reaction to the ingestion of ~20 peanuts over a few hours. Overall, 21% (versus 2% in the placebo group) were able to ingest the 20 peanuts without experiencing an allergic reaction, which is similar to what is also experienced in older age groups (de Silva et al. 2022). However, in the youngest age group (<24 months) 71% could ingest the 20 peanuts without experiencing an allergic reaction and in the oldest age group (36-48 months) only 19% achieved this durable response, suggesting the possibility of high, durable success rates in young children, and potentially a very narrow developmental time window to achieve long lasting benefits from OIT.

Food treatments may have the ability to affect food allergy in important ways other than desensitization and complete remission. There is conflicting data as to whether OIT reduces the frequency or severity of allergic reactions versus usual care, as well as uncertainty about cost-benefit and methodological factors such as the optimal food format, duration, routes of food exposure other than oral, and dose (de Silva et al. 2022). Importantly, the highest patient priority is to reduce severity of reactions from food allergy (Dunlop and Keet 2019). Methodological improvements driven by patient-centered outcomes will continue to improve immunotherapy outcomes(Upton 2022).

***Recent findings in the field of diet and inflammation***

**The implications of nutritional state for COVID-19[[4]](#footnote-5)**

Aging is associated with immune decline (termed immunosenescence) and an increase in low-grade inflammation (termed inflammaging). Immunosenescence is linked with decreased production of new immune cells and reduced function of existing immune cells (Agarwal and Busse 2010). It increases risk and severity of infections (Pera et al. 2015) and results in poorer responses to vaccination (Ciabattini et al. 2018; Goodwin et al. 2006). One of the most noticeable features of COVID-19 has been the susceptibility of older individuals to poorer outcomes, including death. The heightened state of inflammation in older individuals may make them more likely to develop hyperinflammation once infected (“cytokine storm”) and this state is linked to poor outcomes in COVID-19. In those with COVID-19 infection, individuals with the worst outcomes were observed to have a unique profile of metabolites and cytokines along with lower amounts of protective microbes and higher pathobionts(Albrich et al. 2022). Frailty is a loss of resilience and reduced ability to recover from health problems; it is characterised by loss of muscle mass and strength and easy fatigue. Both immunosenescence and low-grade inflammation are worse in frail than non-frail older individuals (Yao et al. 2011) while poor outcomes from COVID-19 are more likely in those who are frail (Zhang et al. 2021b).

Immune impairments have been reported in those living with obesity, such as weakened cell-mediated immunity including antibody responses (Milner and Beck 2012), a heightened state of low-grade inflammation (Calder et al. 2011), increased risk of infections (Huttunen and Syrjänen 2013) and weaker vaccination responses (Neidich et al. 2017). It is now well described that those living with obesity are more susceptible to severe COVID-19 and to mortality from COVID-19 than healthy weight adults (Popkin et al. 2020). Studies from large datasets in the United States and United Kingdom reveal that the adverse effect of body adiposity on COVID-19 outcomes increases across the body mass index (BMI) spectrum (Gao et al. 2021; Kompaniyets et al. 2021). The combination of obesity and a co-morbidity such as type 2 diabetes is likely to result in worse outcomes than obesity alone (Frasca and Bonnie 2020). It could be postulated that adverse effects of chronic low-grade inflammation resulting in adipose-tissue derived factors that suppress immune responses.

The immune system requires sources of energy along with a number of micronutrients and other essential nutrients to function (Calder 2013). It is well-described that micronutrient deficiencies impair the immune system and increase susceptibility to infection (Calder 2020). In the pre-COVID era there was interest in several vitamins (C, D and E) and minerals (iron, zinc, copper, selenium) and immunity where there is quite an understanding of the mechanisms by which those micronutrients support the function of the immune system (Gombart et al. 2020). The roles of vitamins C and D, zinc and selenium have been highlighted in the setting of infection with SARS-CoV-2 and COVID-19 (Abobaker et al. 2020; Griffin et al. 2020; Wessels et al. 2020; Zhang et al. 2020). Although limited effects may be observed with nutrient supplementation in healthy individuals in prevention of respiratory infections, particular subpopulations may benefit (Vlieg-Boerstra et al. 2022). Many studies have reported inverse associations between the status of several micronutrients including vitamins C and D, zinc, and selenium and severity of COVID-19 (Heller et al. 2021; Merzon et al. 2020; Moghaddam et al. 2020) which align with what is known about the important roles of these nutrients in the immune system. Furthermore, low status of micronutrients could be part of the explanation for the susceptibility of older people and those living with obesity to severe COVID-19. However, it is important to identify that the inverse associations that have been reported do not demonstrate cause and effect although often interpreted that way. In fact, some have argued that such studies reflect reverse causality (i.e., SARS-CoV-2 infection causes a decline in micronutrient status that becomes worse as COVID-19 becomes more severe). Cause and effect can be demonstrated through intervention trials. Such trials have been reported in patients with COVID-19 (Annweiler et al. 2020; Carlucci et al. 2020; Entrenas Castillo et al. 2020; Ling et al. 2020; Zhang et al. 2021a) but results are inconsistent. It is important to distinguish between the role of micronutrients in supporting the immune system in the early stages following infection and the use of micronutrients (at high doses) to treat patients who have severe COVID-19.

**Vitamin D and Immune Health[[5]](#footnote-6)**

Many nutrients influence immune health, but vitamin D has generated considerable interest for its pleiotropic effects, including immune modulation (Gombart et al. 2020). Vitamin D is one of the few essential nutrients produced by the body and unlike most other vitamins, it functions as a hormone through the binding of its nuclear receptor (VDR). It has been well demonstrated that the genomic actions of vitamin D regulate immune responses in preclinical experimental models (Ismailova and White 2022). Such models enable the study of vitamin D actions in a highly controlled manner, often in a short timeframe, but with pharmacological concentrations that largely exceed the levels found *in vivo* and poorly reflect the situation observed *in vivo.* Analysis of biospecimens collected during randomized controlled trials (RCTs) has become attractive for extrapolating preclinical studies to *in vivo*. RCTs usually report the effects of vitamin D on clinically relevant outcomes; however, few have addressed the *in vivo* molecular and cellular signatures ofvitamin D interventions. The use of cutting-edge bioanalytical technologies (e.g., single-cell transcriptomics, proteomics, and metabolomics) may offer a comprehensive understanding of how vitamin D functions at the single-cell level and the degree of heterogeneity of these cellular responses. Furthermore, correlations between *in vivo* signatures, serum levels of vitamin D [25-hydroxyvitamin D (25OHD)] and clinical outcomes may provide insight into the required threshold for optimal health outcomes, which, with respect to immune health, remain to be established.

The association between low vitamin D status and many human diseases, including immune-related disorders such as asthma, allergies, and autoimmune diseases, has been replicated many times in various adult and pediatric populations (Mailhot and White 2020; Murdaca et al. 2019). However, RCTs of vitamin D have generally failed to support these associations, contributing to the confusion regarding the benefits of vitamin D on immune health (Ao et al. 2021; Grant et al. 2022). Causal inferences are limited by the possibility of reverse causality and residual confounding, where lower serum 25OHD is a consequence of the disease itself or associated confounders, such as inflammation or limited outdoor activities, resulting in less vitamin D being produced in the skin. Some conditions, such as asthma and chronic obstructive pulmonary disease (COPD), alter cellular vitamin D metabolism by reducing the synthesis of 25OHD and increasing its conversion to 1,25-dihydroxyvitamin D [1,25(OH)2D] (Jolliffe et al. 2020). These individuals may require more vitamin D to achieve optimal 25OHD levels or, alternatively, be treated with 25OHD to bypass the defect in metabolism. Further research is required to clarify how the body handles vitamin D in immune-related disorders.

Vitamin D supplementation increases serum 25OHD, which is highly variable between individuals, and little is known on how individual characteristics (e.g., genetics, age, ethnicity, baseline vitamin D status, weight/BMI, body fat percent, inflammation/disease status) affect the 25OHD response. With the emergence of personalized medicine, a better understanding of the factors influencing response to vitamin D supplementation at the serum, molecular and cellular levels is needed. This will aid in designing personalized dosing schedules (such as a daily low-dose or intermittent high-dose bolus) and effective approaches for optimizing immune health. From a compliance and convenience standpoint, high-dose boluses (e.g., 100,000 IU/month) are advantageous; however, growing evidence suggests that they may be less effective than low-to-moderate daily dosing (e.g., 400 to 1,000 IU/day) (Jolliffe et al. 2021). Physiological responses to such regimens have been investigated with respect to their impact on the circulating levels of various vitamin D metabolites and some health outcomes, but have not been thoroughly studied in various populations and at the mechanistic level (Mazess et al. 2021).

Systematic analyses of clinical materials from high-quality RCTs, biobanking, and global data sharing are strategies that may accelerate research gaps. Collaborative efforts will improve interventions in terms of timing, dose, and efficacy, identify individuals most likely to benefit from the intervention, and provide data supporting evidence-based recommendations that will benefit everyday clinical practice.

**Dietary-related Inflammation and Cancer Risk[[6]](#footnote-7)**

Chronic inflammation plays an important role in the development or progression of several major chronic diseases. For example, IBD increases colon cancer risk and chronic gastritis (due to *Helicobacter pylori* infection) and has been associated with higher risk of gastric cancer. Strong epidemiological evidence exists that non-steroidal anti-inflammatory drugs, particularly aspirin, are powerful chemopreventive agents (Crusz and Balkwill 2015). Diet plays an important role in regulating chronic inﬂammation. Specific dietary factors such as whole grains, vegetables, and certain spices have been shown to have anti-inflammatory properties, whereas other foods such as red meat, processed meat and sugar-sweetened beverages have been shown to have pro-inflammatory properties (Byrd et al. 2019; Kaluza et al. 2018; Tabung et al. 2016). Given that people do not consume foods or nutrients in isolation, nutrition research has shifted from a high focus on single foods or single nutrients to a dietary pattern (whole diet) approach. A dietary pattern is defined as the quantities, proportions, variety, or combination of different foods and drinks in diets, and the frequency with which they are habitually consumed (Sánchez-Villegas and Martínez-Lapiscina 2018). One advantage of the whole diet approach is that it accounts for the complex interactions of the foods, nutrients and bioactive compounds within the dietary pattern, and identifies the net effect of these interactions on health outcomes. Therefore, dietary patterns associated with chronic inflammation may be more predictive of disease outcomes strongly related to inflammation versus the traditional dietary patterns derived without considering inflammatory intermediates (Tabung et al. 2017).

Several dietary indices have been designed to examine the potential of the whole diet to contribute to chronic systemic inflammation in population-based studies. The dietary inflammatory index (DII), a literature-derived nutrient-based index has been associated with risk of and survival from multiple cancers (Li et al. 2018). However, given that the DII is mainly driven by nutritional supplements, it may not be clear if the observed associations are entirely due to the inflammatory potential of the diet or confounded by nutritional supplements. The empirical dietary inflammatory pattern (EDIP) score, based exclusively on whole foods (Tabung et al. 2017), has predicted risk and survival from multiple cancer sites with particularly strong support for colorectal and endometrial cancers, which have been strongly linked with higher obesity (Tabung 2018). Previous studies of EDIP and colorectal cancer suggest that habitual consumption of proinflammatory dietary patterns may deplete cancer-fighting immune cells, thereby increasing susceptibility to cancer initiation and progression. These studies found that colorectal cancer risk was higher among individuals with little to no lymphocytic reaction to the tumor compared with those who had a more robust immune reaction to the tumor suggesting that proinflammatory dietary patterns might contribute to development and progression of colorectal cancer by suppressing the adaptive anti-tumor immune response (Liu et al. 2017). Other studies have suggested additional mechanisms including the interaction between the proinflammatory dietary pattern with the gut microbiome. Diet may be the most important modulator of the gut microbiome and a proinflammatory dietary pattern may adversely affect its composition and function. A study investigated the association between proinflammatory dietary pattern (EDIP assessed) and colorectal cancer subtypes classified by levels of *Fusobacterium nucleatum* in the tumor microenvironment, finding that greater adherence to a proinflammatory dietary pattern was associated with greater risk of *F.* *nucleatum*-positive colorectal carcinomas, but not carcinomas that do not contain these bacteria suggesting that diet-induced intestinal inflammation may alter the gut microbiome to contribute to colorectal carcinogenesis (Liu et al. 2018).

While more mechanistic studies are required for confirmation, collectively these findings suggest that lowering the inflammatory potential of the diet may be preventative for colorectal and other cancers. Dietary pattern interventions to reduce the potential of the diet to contribute to chronic inflammation are therefore warranted to test these strategies for cancer prevention and improved survival.

**Dietary patterns and Inflammatory Bowel Disease[[7]](#footnote-8)**

IBD, characterized by chronic inflammation in the gastrointestinal tract, is increasing globally perhaps because of the adoption of the Westernized lifestyle. Diet, genetics, environment, and the gut microbiome are all etiological factors in IBD, a disease often associated with metabolic consequences. IBD has been associated with dysbiosis, disappearance of butyrate producing bacterial species along with alterations in short chain fatty acids, bile acids and tryptophan metabolites which play a role in the pathogenesis (Lavelle and Sokol 2020).Various dietary factors are known to promote or prevent IBD, an umbrella name of two diseases, Ulcerative Colitis (UC) and Crohn’s disease. The diet, including both quantity and variety, is a complex combination of collective foods and beverages consumed in patterns. However, still only a few studies have considered a whole dietary pattern when studying IBD risk and progression. Indeed a diet with high inflammatory potential does increase risk and symptoms of IBD, unlike a Mediterranean diet pattern (MDP) (Tian et al. 2021). In support of this, the MDP, but not other dietary patterns, has been associated with protection against developing subclinical gut inflammation and a fiber-degrading rich microbiome in first degree relatives with Crohn’s disease patients (Turpin et al. 2022). On the other hand, the Westernized dietary pattern (WDP) is a risk factor for UC (Piovani et al. 2019). Dietary patterns can affect the bioactive compounds produced by gut microbiota, which can impact host health by altering microbiota composition, mucosal immunity and colonic epithelial cell function (Gill et al. 2022). Certainly, foods and beverages like soft drinks, refined sweetened foods, salty snacks, and processed meat, are associated with higher hazard ratios for IBD (Narula et al. 2021). In contrast, white meat, red meat, whole dairy, starch, fruit, vegetables, and legumes were not associated with IBD risk (Narula et al. 2021). Many of these latter foods are included in the MDP, and despite the higher total fat intake and higher saturated fat consumption, the MDP improves IBD onset, and progression (Sasson et al. 2021).

The MDP is rich in plant foods including whole grains, fruits, vegetables, legumes, nuts, seeds, and olives. Olive oil is consumed as the principal source of added fat, along with high to moderate intakes of ﬁsh and seafood, as well as consumption of eggs, poultry, dairy products, and moderate amounts of red meat and red wine during meals. In contrast, the WDP is characterized by vegetable oils rich in mostly omega-6 polyunsaturated fatty acids (PUFAs), processed foods, sweetened beverages, pesticides (such as glyphosate) and food additives. In addition, the WDP is low in protective phytochemicals, dietary fiber, fruits, vegetables, and fish. The increased consumption of a WDP promotes local and systemic inflammation driven by changes in gut microbiota and the immune system, affecting IBD risk. Given the stark contrasting effects on health with the MDP promoting health and the WDP promoting disease, instead of considering removing individual nutrients patients need to be encouraged to consume patterns of food that still include pleasurable food and drinks. This will lead to behavioral changes that allow for lifelong healthy eating habits versus strict dietary exclusion, which can lead to unhealthy relationships with food triggering disordered eating, which is highly prevalent in the IBD population. Therefore, as the nutrition field moves forward, considering dietary patterns or at least combinations of nutrients, such as dietary fiber and fat, should be a key target in future study designs.

**Diet, oxylipins, and inflammation[[8]](#footnote-9)**

Oxylipins are bioactive lipid mediators formed from PUFAs that are found in every cell, tissue, and fluid in the body. The most known oxylipins are those formed from arachidonic acid (AA), but other PUFAs also produce analogous oxylipins which can be similar or different in potency or can have opposing effects to those produced by AA. With the more recent development of high-performance liquid chromatography mass spectrometry (HPLC/MS) methodologies that allow the quantification of hundreds of oxylipins from differing PUFAs, further understanding of the oxylipin balance is emerging (Gabbs et al. 2015).

This emergence is illustrated in the roles of oxylipins in the development and resolution of inflammation. The onset of inflammation in response to tissue damage and/or microbial invasion results in the release of AA-derived oxylipins such as prostaglandin E2, which increases permeability and neutrophil infiltration, and hydroxyeicosatetraenoic acids, which stimulate chemotaxis and chemokine production. Recent research indicates that the resolution of inflammation involves oxylipins called specialized pro-resolving mediators (SPMs), which augment wound healing and enhance neutrophil apoptosis and clearance (Brennan et al. 2021). However, their biological importance has recently been challenged due to questions regarding their formation and activity in immune cells (Schebb et al. 2022). Further, despite originally being seen as pro-inflammatory, it is becoming clear that omega-6 PUFA derived oxylipins have both pro- and anti-inflammatory activities and their roles in immune function remain to be clarified. AA-derived prostaglandin D2, for example, can be both pro- and anti-inflammatory, and epoxy fatty acids derived from AA are vasodilatory, anti-inflammatory and anti-nociceptive (Gabbs et al. 2015).

Dietary PUFAs influence tissue PUFA composition and therefore can influence the oxylipin profile. Oxylipins derived from omega-3 PUFAs more consistently have anti-inflammatory activity, but their precise effects remain to be further understood during the inflammatory response and resolution. Further, although the oxylipin profile usually reflects the tissue fatty acid composition, this is not always true. For example, dietary linoleic acid (LA) level does not alter blood AA levels, but it can alter both LA and AA oxylipin levels (Leng et al. 2017) . Further, it is being appreciated that the predominant dietary PUFAs and essential fatty acids, LA and ALA, also produce oxylipins, and can be a significant portion of the overall oxylipin pool. Thus, further research on these and other understudied and newly discovered oxylipins is needed to further clarify the effects of these biologically active lipid mediators on the immune system.

**Summary and Conclusions**

It is now clear that nutritional status, frailty, vitamin and mineral deficiencies alter the immune response, particularly as we learned during the COVID-19 pandemic. The process of aging is associated with perturbations to immunity, resulting in the production of excessive pro-inflammatory cytokines, vulnerability to infectious agents and poor response to vaccination. Understanding the various triggers that drive this immune dysfunction is key to identifying potential biomarkers of disease and therapeutic targets for older adults. Aging may be related to the gut microbiota, frailty and inflammation that can be mediated by several factors that may evolve as biomarkers. Of all the micronutrients, vitamin D appears to be associated with optimal immune function. Significant progress has been made in the study of vitamin D and its effects on immune health, but gaps remain with respect to in vivo signatures, doses, dosing regimens, target vitamin D levels, and determinants of individual response to interventions in various populations. The therapeutic value of food is illustrated by the application of food-based approaches in the field of food allergy, as observed through OIT. This new food-based method of treating allergy in children is being piloted and used in Canada and OIT is one of the important factors.

Dietary patterns, as opposed to single nutrients or single foods, account for the complex interactions (synergistic and/or antagonistic) of foods, nutrients and bioactive substances ingested in the diet. While the reductionist approach of studying the effects of single nutrients (such as vitamin D) is important, examining the combined effects of nutrients and the interactions of the bioactive components in foods in the context of dietary patterns, will provide a more realistic picture of the effect of the whole diet on human health. This was illustrated by a dietary tool (EDIP) that identifies the inflammatory potential of the diet and has been used in a number of chronic disease studies including cancer and IBD. IBD affects a large portion of the population and has been demonstrated to be responsive to dietary patterns such as the MDP. Finally, the role of oxylipins as biologically active lipid mediators on the immune system provides a mechanistic insight into the body’s inflammatory response to various triggers. Although much has been identified in this field there are still many questions that need to be answered. Future research should focus on several gaps and key areas identified during this conference (Figure 1 and Table 1).

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**CL Dunbar:** Writing – original draft; Writing – review & editing

**HM Aukema:** Writing – original draft; Writing – review & editing

**PC Calder:** Writing – original draft; Writing – review & editing

**DL Gibson:** Writing – original draft; Writing – review & editing

**SE Henrickson:** Writing – original draft; Writing – review & editing

**S Khan:** Writing – original draft; Writing – review & editing

**G Mailhot:** Writing – original draft; Writing – review & editing

**S Panahi:** Writing – review & editing; Visualization; Conceptualization

**FK Tabung:** Writing – original draft; Writing – review & editing

**M Tom:** Writing – review & editing; Conceptualization

**JEM Upton:** Writing – original draft; Writing – review & editing

**DA Winer:** Writing – original draft; Writing – review & editing

**CJ Field:** Writing – original draft; Writing – review & editing; Supervision; Conceptualization

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**Figure Caption**

**Figure 1:** A selective snapshot of key findings and recommended areas of research identified by experts that participated in the 2022 Canadian Nutrition Society symposium (Created with Canva.com).

1. Section written by Dan Winer and Saad Khan [↑](#footnote-ref-2)
2. Section written by Sarah Henrickson [↑](#footnote-ref-3)
3. Section written by Julia Upton [↑](#footnote-ref-4)
4. Section written by Philip Calder [↑](#footnote-ref-5)
5. Section written by Geneviève Mailhot [↑](#footnote-ref-6)
6. Section written by Fred K. Tabung [↑](#footnote-ref-7)
7. Section written by Deanna Gibson [↑](#footnote-ref-8)
8. Section written by Harold Aukema [↑](#footnote-ref-9)