Abstract

Evidence suggests that periods of heavy intense training can result in impaired immune cell function, whether this leaves elite athletes at greater risk of infections and upper respiratory symptoms is still debated. There is some evidence that episodes of upper-respiratory symptoms do cluster around important periods of competition and intense periods of training. Since reducing upper respiratory symptoms, primarily from an infectious origin, may have implications for performance, a large amount of research has focused on nutritional strategies to improve immune function at rest and in response to exercise. Although there is some convincing evidence that meeting requirements of high intakes in carbohydrate and protein and avoiding deficiencies in nutrients such as vitamin D and antioxidants is integral for optimal immune health, well-powered randomised controlled trials reporting improvements in upper-respiratory symptoms beyond such intakes are lacking. Consequently, there is a need to first understand whether the nutritional practices adopted by elite athletes increases their risk of upper respiratory symptoms. Second, promising evidence in support of efficacy and mechanisms of immune-enhancing nutritional supplements (probiotics, bovine colostrum) on upper respiratory symptoms needs to be followed up with more randomised controlled trials in elite athletes with sufficient participant numbers and rigorous procedures with clinically relevant outcome measures of immunity.

Highlights

- Evidence suggests that upper-respiratory symptoms in athletes typically cluster around intense periods of training, with greater risk during the winter months.

- Emerging evidence supports the use of probiotics and bovine colostrum to enhance immune health and reduce URS, to further elucidate mechanisms and efficacy well-powered randomised control trials in athletes are warranted
- Exercise in a state of mild hypohydration (1-3%) may not detrimentally affect mucosal immunity, with little evidence for an association between hypohydration and self-reported URS
- Randomised control trials to establish how periodised carbohydrate intake can impact self-reported URS and *in-vivo* measures of immune function in athletes are warranted
- Limited evidence to support to the use of protein and amino acid supplementation to reduced URS
- Antioxidant and vitamin D supplementation may be warranted in those who are deficient and exposed to extreme unaccustomed acute physical stress, however randomised control trials tracking changes in URS and immunological markers in athletes are needed.

Key words

Immunology, Nutrition, Exercise

Introduction

The relationship between infection risk and exercise training load has long been described as a J-shaped curved (Figure 1), with high training loads believed to increase the risk of opportunistic infections, particularly of the upper respiratory tract (Nieman, 1994). However, there is limited empirical evidence that elite athletes experience more infections than the general population (Svendsen, Taylor, Tonnessen, Bahr & Gleeson, 2016). Based on re-

evaluation of published data, Malm (2006) proposed that elite training is associated with a lower susceptibility to infection compared to high exercise workloads, whereby the relationship between infection risk and training load instead resembles an S-shaped curve (Figure 1)(Malm, 2006). Whilst this remains to be verified in prospective studies, it is hypothesised that to maintain elite athlete status there is a pre-requisite to have a robust immune system capable of withstanding infections even during heightened physical and psychological stress. However, it may be that the reduced infection risk in elite athletes observed in previous studies may not reflect a lower impact of physical stress (exercise workload) per se but rather a reflection of better preventive and treatment strategies in place within the studied elite settings. Nevertheless, although elite athletes may not experience a greater annual incidence rate of infections, there is increasing recognition that episodes of upper-respiratory symptoms (URS) typically cluster around intense periods of training (Hellard, Avalos, Guimaraes, Toussaint & Pyne, 2015; Moreira, Delgado, Moreira & Haahtela, 2009; Svendsen, Gleeson, Haugen & Tønnessen, 2015; Svendsen et al., 2016) with a greater risk during winter months (Hellard et al., 2015; Spence et al., 2007).

URS is the most common medical complaint affecting athletes, and with medals often being decided by the smallest of margins, even minor illnesses can have a meaningful, negative impact on competition outcomes. Indeed, fewer days of illness appears to be one factor that differentiates World and Olympic medallists from other international-level athletes (Svendsen et al., 2015). URS in athletes is likely to involve both infectious and non-infectious causes, previous reports suggest between 31% (Spence et al., 2007) and 82% (Hanstock et al., 2016) of URS episodes during winter months occur with an infectious pathogen. Non-infectious URS in athletes may be related to allergic rhinitis, asthma and/or exercise-induced bronchoconstriction.

Since reducing URS, particularly of infectious origin, may have implications for athletic performance, it is not surprising that a large amount of research has focused on nutritional strategies to improve immune function at rest, and/or favourably modify the immune response to exercise. Although the impact of a chronically high training load on immune function is still debated, it is documented that a single bout of prolonged, intense exercise transiently modifies a large number of immune variables. Following intense exercise an individual's capacity to defend against pathogens is altered, resulting in what is referred to as an "open window" for infectious causes of URS, lasting up to 72 hours post-exercise depending on the intensity and duration of the exercise, and the immune marker measured (Moreira et al., 2009).

Quantifying immunocompetence in athletes in the field and identifying changes that predict infection risk as a result of interventions is challenging. The gold standard (or most relevant outcome) may be clinical symptoms such as whether or not an individual actually contracts an infection, as confirmed by pathological tests, assuming that pathogen exposure is similar across intervention groups. However, in order to elucidate the underlying mechanisms that mediate any potential changes in infection risk following a nutrition intervention, it would also be pertinent to include immunological markers in laboratory research trials.

This short review will provide an updated summary on selected immune nutrition topics including dietary carbohydrate and protein intake, hydration status, antioxidants, vitamin D, bovine colostrum, and probiotics, including when evidence is available practical recommendations for the sport and exercise nutrition practitioner and/or athlete and coach (Table 1). For a more in-depth review, readers are referred to the latest consensus statement of the ISEI (Bermon et al., 2017).

Carbohydrate

It is well documented that carbohydrate intake is a fundamental part of an athlete's diet, both in its ability to enhance physical performance and its role in recovery following exercise. Athletes adopting a train-low compete-high CHO intake approach may increase their risk of immune impairment during periods of restricted CHO intake (Burke, 2010). Previous work has shown that participants on low carbohydrate diets (less than 10% of energy from CHO) for 48 – 72 hrs have larger circulating stress hormone (cortisol, adrenaline) and cytokine (IL1ra, IL6, IL10) responses when compared to normal or high CHO diets (Bishop, Walsh, Haines, Richards & Gleeson, 2001b). Whilst it should be noted that it is unusual for elite athletes to regularly have intakes as low as that outlined in the Bishop paper (<10% of daily energy intake from CHO equated to ~1.1 g/kg body mass per day); it is not unheard of for this to be the case for short periods. Athletes may adopt a low CHO intake lasting 1-3 days in specific scenarios e.g. making weight or during periods of tapering where training volume may decrease for competition preparations (Reale, Slater & Burke, 2017). In contrast, high CHO diets have been associated with blunted plasma cortisol responses to exercise due to preservation of plasma glucose, better maintenance of post-exercise plasma glutamine concentrations and attenuated exercise-induced disturbances in the number of circulating leukocytes, neutrophils and lymphocytes (Bishop, Walsh, Haines, Richards & Gleeson, 2001a; Gleeson, Blannin, Walsh, Bishop & Clark, 1998).

The majority of evidence from the literature suggests that increasing CHO availability will act indirectly to reduce the stress hormone response to exercise and therefore limit exercise-induced immune impairment. There is also some evidence to suggest the beneficial effects of consuming CHO during exercise can occur without any effect of plasma cortisol levels, although this is likely to be dependent upon intensity and duration (Green, Croaker & Rowbottom, 2003). Sixty grams per hour of CHO attenuates the rise in plasma cytokines during exercise, and reduces the trafficking of leukocyte subsets during prolonged (2.5h) endurance

running (Henson et al., 1998). In contrast, however, CHO feeding during marathon running appears ineffective in altering salivary secretory immunoglobulin-A secretion and reducing self-reported symptoms of URS (Nieman et al., 2002). Recent evidence also found that acute CHO ingestion before, during and after prolonged exercise had no benefit on in vivo immune responses with a novel antigen (Davison, Kehaya, Diment & Walsh, 2016).

Whilst a substantial body of evidence supports the influence of carbohydrate availability (in terms of dietary intake or acute supplementation) on stress hormone responses and in vitro markers of immune function (Bishop, Walsh, Haines, Richards & Gleeson, 2001a; Gleeson et al., 1998), evidence is lacking with use of clinically relevant outcomes (integrated in vivo measures, incidence of URS). Despite the lack of studies showing a benefit of CHO on URS it is important to acknowledge that CHO intake and supplementation have consistently been shown to enhance aspects of performance and recovery. Subsequently if athletes achieve recommended intakes for CHO (Table 1) during training and competition, it may help control for any proposed impact of CHO availability on immune function. Periodised CHO intake to match training intensity and competition with periods of restriction to enhance training adaptations (Bartlett, Hawley & Morton, 2015; Burke, 2010) could offer a suitable compromise between fuelling and enhancing training adaptations and limiting the negative effects of low CHO availability upon the stress hormone response.

Protein

Immune function is reliant on rapid cell replication and generation of proteins such as cytokines and immunoglobulins. It is therefore not surprising that inadequate protein intake has been associated with compromised host defence and susceptibility to opportunistic infection. Although athletes typically appear to consume adequate amounts of protein, some individuals

may experience sub-optimal protein intake, for example during periods of heavy training and/or weight loss. Even in endurance athletes meeting the recommended daily protein intake of 1.6 g/kg body mass (Tarnopolsky, 2004), there may be immunological benefits of further increasing dietary protein during intense training periods. Witard et al. (2014) found that during intensified training increasing daily dietary protein intake from 1.5 to 3 g/kg body mass (whilst maintaining a carbohydrate rich diet of 6 g/kg body mass per day) blunted the exercise-induced impairment in CD8+ T lymphocyte, total leukocyte and granulocyte redistribution observed in participants following a lower protein diet (Witard et al., 2014). Importantly the high protein diet resulted in significantly fewer self-reported URS, with the authors proposing that consumption of a high protein diet may help maintain immune surveillance during high-intensity training. The exact dose for optimal immunological benefits during periods of intensified training may be somewhere between 1.5 and 3g/kg body mass, depending on the type of exercise conducted, but further research is warranted to establish clearer recommendations.

There has also been interest in single amino acid supplementation to influence immune competence in athletes. Specifically the non-essential amino acid glutamine is an important fuel for immune cells in particular lymphocytes and macrophages (Castell & Newsholme, 1997). Endurance exercise can reduce plasma glutamine (Castell & Newsholme, 1998) and it has been hypothesized that oral glutamine supplementation may enhance post-exercise immunity (Castell & Newsholme, 1997). However, the majority of studies have found that reduced plasma glutamine does not meaningfully contribute to exercise-induced immune impairment (Gleeson, 2008). Despite an attractive hypothesis, there is little evidence that glutamine supplementation influences immune responses to exercise.

There remains a lack of randomised controlled trials assessing increased protein intake upon self-reported URS, and despite some mechanistic evidence for glutamine supplementation

showing immune benefits, to date there is limited evidence that glutamine supplementation is effective in abolishing the post-exercise immune cell impairment and URS.

Hydration

It is not unusual for athletes to commence training in a pre-existing fluid deficit. A combination of factors can lead to this predisposition, including failure to rehydrate between sessions or specific weight making strategies. The potential negative effects of hypohydration during exercise in laboratory settings are well documented; increased cardiovascular strain, elevated core temperature and increased perception of effort (Sawka & Coyle, 1999). Furthermore, a pre-exercise fluid deficit of as little as a 1.5-2.0% body mass loss (BML) has been suggested to negatively affect laboratory based exercise trials (Maughan & Shirreffs, 2004). In contrast, recent evidence suggests that in appropriate and representative environmental conditions of outdoor exercise where effective evaporative cooling can be maintained body mass losses of up to 3% can be well tolerated and have little negative impact upon exercise performance (Wall et al., 2015).

With regard to the immune response to moderate hypohydration there appears to be no negative effect on total or differential leukocyte numbers, lymphocyte function (Mitchell, Dugas, McFarlin & Nelson, 2002), neutrophil function, or antigen-stimulated cytokine production (Svendsen, Killer & Gleeson, 2014). As such, undertaking exercise in a hypohydrated state, at least within the range generally applicable to athletes, does not appear to have meaningful implications for cellular immunity.

In contrast, significant reductions in salivary flow rates have been observed in exercising participants at a BML of 1.3-3% (Killer, Svendsen & Gleeson, 2015). Saliva contains numerous antimicrobial proteins (AMPs) that play an important role in mucosal immunity, and reductions

in salivary flow rate may therefore have implications for host defence. To date, secretory IgA (SIgA) has been the most studied marker of mucosal immunity within athletic populations. The importance of salivary lysozyme (SLys) and salivary lactoferrin (SLac) have also gained recognition as both are present in mucosal secretions of the upper respiratory tract and understood to play an integral role in the innate immune system.

Fortes and colleagues investigated SIgA and SLys following exercise-induced dehydration and subsequent overnight fluid restriction (3% BML) (Fortes, Diment, Di Felice & Walsh, 2012). Dehydration resulted in a significant decrease in SIgA concentration, with no change in secretion rate and conversely, no change in SLys concentrations but a significant reduction in secretion rate. Research has also identified transient changes in salivary AMPs during and immediately post-90 min exercise following 24 h fluid restriction, which had mostly returned to baseline values by 3 h post-exercise (Killer et al., 2015). Exercise in a state of mild hypohydration caused a reduction in saliva flow rate, yet induced greater secretion rates of SLac and higher concentrations of SIgA and SLys.

These data suggest that prolonged exercise in a state of mild hypohydration (1-3%) may not detrimentally affect mucosal immunity. Whilst there remains a lack of evidence into incidence of URS and hydration status, it is unlikely that the reported small transient fluctuations in salivary AMPs would translate into clinical relevance. Furthermore, inconsistencies in the measurement of AMP concentrations vs secretion rates, variation in dehydration protocols (fluid restriction vs exercise-induced) and a wide range of levels of dehydration (percentage BML) are likely to contribute to the lack of clarity around the impact of hydration on mucosal immunity, in particular when deciphering any clinical significance. Future research should look to address some of these issues and establish if exercise-induced hypohydration in a range of environments (laboratory and field) can have a detrimental impact upon exercise-induced immune impairment.

Antioxidants

Strenuous exercise is associated with an acute increase in the production of free radicals (reactive oxygen species (ROS), and reactive nitrogen species (Powers, Nelson & Hudson, 2011). An endogenous network of enzymatic (e.g. superoxide dismutase, glutathione peroxidase, catalase) and non-enzymatic antioxidants (e.g. vitamins A, C and E) exist to provide intracellular and extracellular protection against oxidant damage (Powers, Deruisseau, Quindry & Hamilton, 2004). Whilst it is acknowledged these antioxidant defences adapt with training, it has long been debated whether they are sufficient to counter oxidant production during strenuous exercise. Early investigations highlighting the damaging effects of oxidants on muscle and cells led to a proposed role of antioxidant status in exercise-induced immune dysfunction following prolonged exercise (Powers et al., 2011).

Of all the potential exogenous antioxidant supplements, the essential nutrient vitamin C has received the greatest attention as a strategy to support immune health in athletes (Nieman et al., 2002). Initially, interest was also partly due to preliminary evidence of the prophylactic benefit of vitamin C on the common cold. The current evidence, however, provided by the latest Cochrane review, reports that routine vitamin C supplementation (> 0.2 g per day) does not reduce the risk of developing a cold in the general population but such regular supplementation (as opposed to upon onset of symptoms) appears to reduce the duration and severity of colds (Hemilä & Chalker, 2013). In contrast, pre-specified sub-group analysis of trials in this review concluded that there is firm evidence that vitamin C supplementation between 0.25 and 1.0 g/day results in reduced number of participants reporting URS under periods of physical stress with or without cold stress (marathon runners, skiers and soldiers on subarctic operations). The underlying mechanism(s) of such effects remains unclear,

particularly as any role of exercise-induced oxidant production in alterations of immune dysfunction has not been shown consistently (Nieman et al., 2002). Additional evidence has purported benefits of vitamin C in non-infectious causes of URS (e.g. exercise-induced bronchoconstriction) following exercise (Hemilä, 2013).

Investigation of other essential nutrients with antioxidant potential (e.g. vitamin E) or multiple vitamins have largely been unsuccessful with concerns over pro-oxidant/pro-inflammatory effects in large doses or interference with the role of ROS in key signalling processes of training adaptation (Nieman & Mitmesser, 2017). Focus in this area has shifted towards other nutritional compounds in the human diet such as polyphenols, albeit the emerging evidence of the effects of these interventions on URS risk in athletes also appear to be independent of any antioxidant properties (e.g. direct anti-pathogenic pathways) (Somerville, Braakhuis & Hopkins, 2016). There is lack of conclusive evidence that exercise-induced oxidant production is detrimental to athlete health, including host defence. Nevertheless, the additional evidence of the effect of vitamin C on duration and severity of URS means evaluation on an individual athlete basis may be clinically worthwhile. The evidence of higher regular intake of vitamin C and reduced incidence of URS, however, should not be ignored. It is important to stress that these benefits were evident within a range of doses (0.25 – 1.0 g per day) that were not particularly high, and thus excess consumption may be easily achieved through use of over-the counter vitamin C supplements. It appears that these benefits are only apparent in those exposed to short-term unaccustomed physical stress. Such findings may have limited application to the trained athlete who has regular (long-term) exposure to such stress (i.e. training and competition).

Vitamin D

Over the past decade, there has been emerging evidence highlighting the role that vitamin D may have in athlete health (Owens, Fraser & Close, 2015). Commonly known for its role in bone health (Ebeling, 2014) and muscle function (Owens et al., 2015) it is also increasingly recognised for its role in inflammation and aspects of innate and acquired immunity (He et al., 2016).

Unlike other vitamins that are primarily obtained through diet, physiological sufficiency for vitamin D can be met through endogenous synthesis via UV irradiation of the skin's dermis. The cutaneous production of vitamin D is highly variable and dependent upon both environmental and individual factors. These include season, time of day, amount of cloud cover, skin pigmentation, age, clothing, and use of high-factor sunscreen (Chen et al., 2007). Furthermore, vitamin D synthesis drops in winter months at latitudes greater than 35-37° due to insufficient UVB photons reaching the Earth's surface (Webb, Kline & Holick, 1988).

Adequate concentration has been previously defined as serum 25 hydroxy vitamin D (25(OH)D) >50 nmol/L by the US Institute of Medicine. However, within the literature, there is a lack of consensus as to what constitutes vitamin D deficiency and what might be classified as an insufficiency for elite athlete health and performance. It is beyond the scope of this review to discuss what constitutes sufficient or optimal circulating concentrations of 25(OH)D, so readers are referred to He et al (2016) for more information (He, Aw Yong, Walsh & Gleeson, 2016). The prevalence of deficiency and sufficiency in athletes varies by, training location, sport (Larson-Meyer & Willis, 2010) and skin colour (Pollock, Dijkstra, Chakraverty & Hamilton, 2012), with deficiency being greater in the winter months (Farrokhyar et al., 2015). There is growing evidence that vitamin D likely plays a key role in both innate and acquired immunity through its modulation of gene expression (Kamen & Tangpricha, 2010). Vitamin D upregulates gene expression of antimicrobial peptides, which are important regulators in innate immunity, and downregulate expression of inflammatory cytokines (He et al., 2016).

Furthermore, vitamin D is also found to have an immunomodulatory effect on T and B-lymphocytes in acquired immunity (Von Essen et al., 2010).

A small number of studies have reported negative associations between vitamin D concentration and self-reported URS in athletes (He et al., 2013) and military personnel (Laaksi et al., 2007). In a study of endurance athletes, those in a Vitamin D deficient status group 25(OH)D < 30nmol/L), reported greater number of URS days and higher symptom-severity scores compared to counterparts with greater circulating vitamin D concentrations (He et al., 2013). Elite athletes reporting with URS who had a positive virology/bacteriology result (infectious group) or athletes with a mild to moderate leucocytosis (suggestive group) had significantly lower levels of circulating 25(OH)D levels than athletes with a negative virology/bacteriology count and normal differential leukocyte count (Cox et al., 2008). In a military setting young Finnish conscripts who had low circulating 25(OH)D concentrations (defined by the authors as <40 nmol/L) had significantly more duty days lost to respiratory infection during 6 months of training and were 1.6 times more likely to miss duty due to respiratory infection than those with a circulating 25(OH)D >40 nmol/L (Laaksi et al., 2007).

Although causality cannot be established from these cross-sectional comparison studies of physically active individuals, they are in agreement with RCTs of general populations that show reduced respiratory infections with daily or weekly vitamin D supplementation, particularly in those with deficiency (< 25-30 nmol/L circulating 25(OH)D) (Berry, Hesketh, Power & Hyppönen, 2011).

Bovine colostrum

Bovine colostrum (COL) is the initial milk produced by a cow in the first few days following parturition. In addition to a different composition of macronutrients (higher percentage of

protein, lower percentage of lactose and fat) compared to mature milk (Ontsouka, Bruckmaier & Blum, 2003), COL is richer in antimicrobial, growth and immune factors (Uruakpa, Ismond & Akobundu, 2002). In fact, the bioactivity of COL is at its greatest in the first milking with the concentrations of such components decreasing over the subsequent days (Korhonen, Marnila & Gill, 2000). Although sharing a homologous composition to human colostrum, the concentrations of immune factors in COL are in vastly greater concentrations (Shing, Peake, Suzuki, Jenkins & Coombes, 2013). Such bioactivity has led to suggestions that COL could enhance human immune function and hence aid prophylaxis of infections.

A recent meta-analysis (Jones, March, Curtis & Bridle, 2016) of five randomised controlled trials concluded COL supplementation reduces the incidence rate of episodes and total number of days of URS during exercise training (cyclists, distance runners, recreational athletes, swimmers). The magnitude of these reductions (URS days: 44%; URS episodes 38%) are greater than the smallest clinically important difference, but the low precision of the individual study estimates (as a result of small sample sizes and hence low number of events) means that further trials will likely change the best estimate of the average effect of COL. The minimum and/or the optimum dose of COL for benefit on incidence of URS is yet to be confirmed, but there is preliminary tentative (observational) evidence suggesting 20 g per day may result in superior protection than 10 g (Jones et al., 2016) (Table 1). There remains a lack of evidence to determine whether COL supplementation can reduce duration or severity of URS episodes in athletes.

Given the somewhat uncertainty surrounding the causes of self-reported URS with exercise, there may be a number of potential mechanisms responsible for the effects of COL on URS during exercise training. In-depth reviews of the underlying mechanisms in the effects of COL have been discussed extensively elsewhere (Bermon et al., 2017; Davison, 2012). Briefly, one proposed mechanism is that the small bioactive constituents of COL, or their metabolites,

appear in the circulation after consumption and have immune-enhancing effects on host immunity (Jones et al., 2016). Recently, COL supplementation induced greater sensitivity of in vivo immune responses to a novel antigen (experimental CHS) following prolonged exercise (Jones et al., 2018). Whilst recognising that the specific mechanisms of action of COL may differ between populations, reports of reduced incidence of respiratory infections in other at risk groups (with immune deficiency/recurrent infections) are further examples of available evidence supporting an hypothesis that use of COL can lead to changes in host defence against pathogenic causes of URS (Cesarone et al., 2007; Patıroğlu & Kondolot, 2013).

Probiotics and Prebiotics

The human intestine represents the largest mass of lymphoid tissue in the body and is resident to thousands of bacterial taxa (Wylie et al., 2012). The adult gastrointestinal immune system comprises of a stable alliance among the commensal microbiota, immune mediators, and the epithelial barrier. All three components are essential for function and maintenance of a stable and mature intestinal immune system. Nutritional supplementation to support the gut microbiota is a proposed means to maintain immune competence and reduce URS risk (Hao, Dong & Wu, 2015).

It is now recognised that the species composition of the microbiota can be modified by alterations in dietary intake. Regular consumption of probiotic bacteria can positively modify the composition of the gut microbiota and influence immune health (Round & Mazmanian, 2009). Alternatively, a prebiotic, a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microbiota can confer benefits upon host well-being and health (Gibson et al., 2017). However, to date there are currently no published studies on the efficacy of prebiotics to reduce URS in athletes. Non-

infectious causes of URS such as exercise-induced bronchoconstriction has shown a favourable response to prebiotics (Williams et al., 2016).

A large number of studies have been conducted investigating the effects of probiotics on URS in the non-athlete general population, and readers are referred to the latest Cochrane systematic review for more detail (Hao et al., 2015). The review concluded that probiotics were better than placebo with fewer participants experiencing at least one episode of acute URS, but there was no difference when measuring rate of episodes of URS or the duration of episodes (Hao et al., 2015).

With regard to probiotic use and athletes, there are few well-conducted large scale randomised controlled trials, but readers are referred to a 2015 review of the probiotic literature in athletes for more detail (Pyne et al., 2015). Briefly, they identified 15 relevant experimental studies from 2006 to 2014 that investigated the clinical and immunological effects of probiotic supplementation in trained individuals; five randomised placebo controlled studies reported reductions in self-reported URS frequency, with three reporting trivial to no effects (Pyne et al., 2015).

A randomised crossover trial showed benefit from a daily dose of $1.3x10^{10}$ colony forming units (CFU) *Lactobacillus fermentum* for 28 days in distance runners during a winter training period (Cox, Pyne, Saunders & Fricker, 2010). The number of days, and severity of self-reported URS was less (~50%) in those receiving the probiotic compared to placebo. This was coupled with a two-fold greater change in whole blood culture interferon-γ with the probiotic; however, there were no changes in salivary IgA, or IL-4 and IL-12 (Cox et al., 2010). Further evidence in support of probiotic feeding showed that 16 weeks of *Lactobacillus casei Shirota* ($1.3x10^{11}$ cells per day) reduced the proportion of active individuals reporting URS by 36%, reduced the number of URS episodes (1.2 vs 2.1), and increased salivary IgA over the course

388 of the study (Gleeson, Bishop, Oliveira & Tauler, 2011). However, there was no difference in
389 duration of symptoms (Gleeson et al., 2011). In contrast, a follow up study using a probiotic
390 bacteria strain of *Lactobacillus salivarius*, $2x10^{10}$ CFU for 16 weeks failed to reduce the
391 frequency of URS in an athletic cohort or modify markers of immune function (Gleeson et al.,
392 2012), highlighting issues with strain specificity. Further issues arise with potential sex
393 differences in responsiveness to probiotic treatment as 11 weeks of *Lactobacillus fermentum*
394 ($1.0x10^9$ cells per day) was able to reduce illness load (severity x duration) of URS by 31% in
395 males but not females (West et al., 2011).

396 It appears there is a growing body of evidence that probiotic supplementation may be beneficial
397 in reducing the frequency of URS during periods of high training load. A greater number of
398 well-controlled studies with probiotics are required to clarify dose response, strain choice and
399 elucidate mechanisms of action within athlete populations. Furthermore, prebiotics, which act
400 by increasing the growth and activity of non-pathogenic commensal bacteria at a genus level
401 maybe a viable alternative or have an additive effect as a synbiotic (combined probiotic and
402 prebiotic intervention) and research into their use is warranted.

403

404 ***Conclusions***

405 The risk of URS in athletes typically cluster around important periods of travel, competition
406 and intense periods of training. In order to limit the detrimental effects of URS on training
407 completion or competitive performance, elite athletes seek strategies to prevent or manage such
408 events. There is a need to understand whether the nutritional practices adopted by elite athletes'
409 increase their risk of URS. The nutritional interventions discussed in this review show some
410 promising mechanistic evidence for an immunomodulatory effect within athletes, yet well-
411 powered randomised controlled trials reporting reduced incidence in URS are not widely

available. There is need for more randomised controlled trials to establish the efficacy of nutrient interventions in elite athletes with sufficient participant numbers, rigorous procedures and use of validated assessment of clinical symptoms confirmed with pathological tests where appropriate. Studies investigating interventions with purported immune modulatory mechanisms of action are recommended to couple measurement of URS with clinically relevant outcome measures of immunity.

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629 Table 1 summary of the effects of nutritional interventions on upper respiratory symptoms in athletes and practical recommendations

Nutrient	Markers of immune function			Clinical symptoms (URS)	Research recommendations	Practical recommendations
	In vitro	Ex vivo	In vivo			
CARBOHYDRATE	[✓]	[✓]	[×]	○○○○○ Lack of RCTs investigating effect on URS	Further RCTs to establish if training in a low CHO state or CHO feeding during and after prolonged exercise impacts on URS and integrated in vivo measures of immune function	Athletes consuming 30–60 g CHO per hour during sustained intensive exercise will aid the demands of physical and metabolic recovery. Immediately post exercise (0-2 hours) athletes are recommended to consume 1.0-1.2 g/kg body mass, however the absolute amount should be adjusted depending on the nature of the training session they have completed and the duration of the recovery period before the next training session. These intakes may attenuate the rise in stress hormones and indirectly limit the degree of exercise-induced immune impairment. Athletes undergoing train-low strategies should carefully periodise these sessions within their season to limit any potential impact this may have on immunity and thus on their ability to perform in competition.
PROTEIN/AMINO ACIDS	[✓]	[✓]	[×]	⊙○○○○ Limited number of RCTs showing benefit of additional total protein or glutamine supplementation.	Further RCTs to establish if additional total protein or glutamine supplementation impacts on URS and integrated in vivo measures of immune function	Athletes are recommended to consume adequate daily amounts of protein (1.2 - 1.7 g/kg body mass), depending on the nature of their training, to help maintain sufficient whole body protein metabolism. Subsequently this may support correct immune function. It should also be noted that the pattern of ingested protein can affect whole-body protein metabolism, ~20-30 g at regular (~3 h) intervals throughout the

						day is recommended for maximising net protein balance. Further supplementation of protein intake or single/multiple amino acids is not recommended to improve immunity and reduce URS incidence.
HYDRATION	[✓]	[?]	[×]	○○○○○ Lack of RCTs investigating effect on URS	Lack of evidence for an association between hypohydration and self-reported URS, future research should look to establish if higher levels of hypohydration can impair immune function and if this is environment dependent.	Athletes should be advised to maintain fluid balance throughout day-to-day training to ensure optimal performance and health, especially when away at training camps either in the heat or at altitude where fluid losses may be elevated, and infection risk increased. Daily monitoring of body mass during training camps is a simple and inexpensive method commonly used to monitor changes in fluid balance. In addition, regular monitoring of either urine osmolality or specific gravity can indicate normal ranges for individual athletes and therefore highlight fluid imbalances quickly and effectively.
ANTIOXIDANT SUPPLEMENTATION	[✓]	[✓]	[×]	⊙⊙⊙○○ Meta-analysis of RCTs of heavy acute exercise (and/cold) stress	Given the lack of evidence of vitamin C supplementation to reduce reporting URS in general population, further RCTs are needed during periods of short-term and long-term physical stress with changes in URS supported by clinically relevant immunological markers.	Athletes are recommended to consume a nutrient-dense diet with a variety of fresh fruits and vegetables. In the absence of any rare nutritional (e.g. vitamin C) deficiencies, most athletes are recommended to avoid excessive supplementation with antioxidant vitamins. Supplementation of 0.25 – 1.0 g/day of vitamin C to reduce URS may be useful in some athletes when exposed to extreme unaccustomed acute physical stress.
VITAMIN D SUPPLEMENTATION	[✓]	[✓]	[×]	⊙⊙⊙○○	RCTs of vitamin D supplementation (to correct deficiency) to establish	Practical recommendations seem to be effective in those who are deficient (< 30 nmol/L) and these can be made for both summer and winter months,

				Meta-analyses of RCTs in general population	whether effect on URS in other populations can be shown in athletes. Assessment of URS should be supported by integrated in vivo measures of immune function	although considerations must be made for latitude and skin type. Seasonal screening for vitamin D deficiency is recommended throughout the year in athletes. Bespoke strategies can then be put in to place which either involve maintenance (1000 - 2000 IU/day) or increasing intake to reverse a deficiency. Studies show that consuming a 1,000 to 2,000 IU/day vitamin D3 supplement during winter can achieve sufficiency in most individuals. However, up to 4,000 IU/day may be needed if starting from deficiency. Furthermore, those training indoors or individuals required to wear protective or religious clothing in the summer may also benefit from the 1,000 IU/day vitamin D3 recommendation. In the absence of deficiencies, most athletes are recommended to avoid excessive intake of vitamin D.
BOVINE COLOSTRUM	[✓]	[✓]	[✓]	⊙⊙⊙⊙O Meta-analyses of RCTs in athlete populations	Low precision of estimates of effect on URS need to be followed up with appropriately designed and adequately powered RCTs. Key mechanisms of action need to be elucidated.	Consider daily supplementation (10-20 g) of bovine colostrum particularly during periods of greatest URS risk (e.g. winter period, training camps, long haul travel and competition).
PROBIOTICS	[✓]	[✓]	[?]	⊙⊙⊙⊙O Numerous RCTs in athletes and meta-analyses of	Well-controlled research studies are required to establish dose and strain specific responses of probiotic interventions. Furthermore,	To ensure colonisation of bacterial species in the gut, implementation of probiotic supplementation is recommended to commence at least 14 days prior to overseas travel or competition. With a strain specific consensus lacking, a multi-strain probiotic

				RCTs in general population	mechanisms in elite athletes need to be elucidated. A viable alternative treatment may be a synbiotic (combined probiotic and prebiotic intervention) and research into their use is warranted.	combining species from the genus's lactobacillus and bifidobacterium with the viable number of cells per species greater than $1x10^9$ CFU per day should be considered to ensure the greatest survival to the gut, and subsequent immune modulation.

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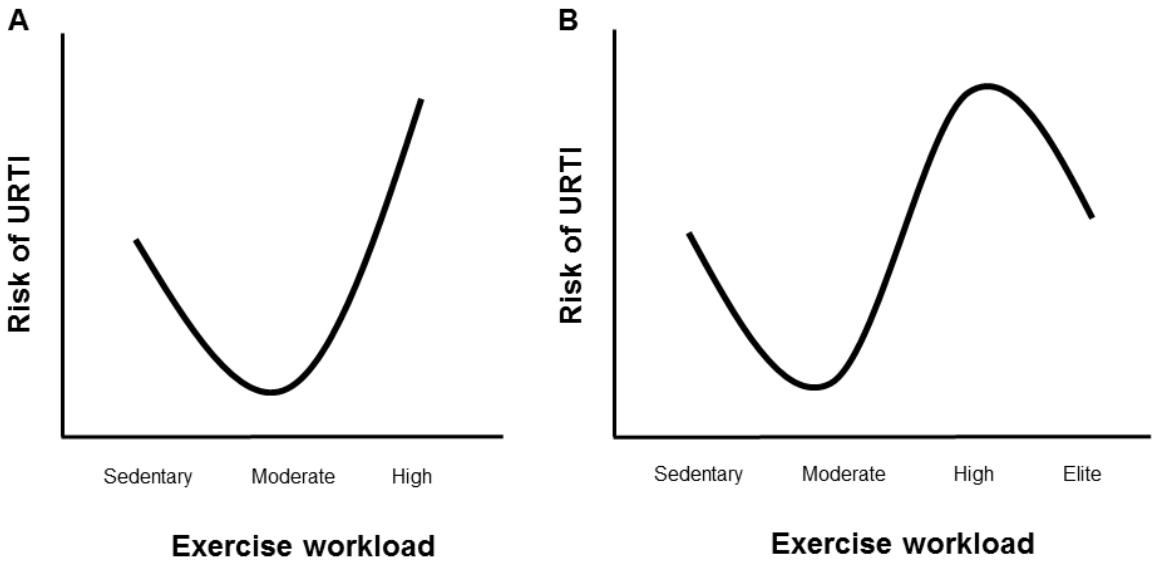

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633 Figure 1 The proposed J-shaped (A) (Nieman, 1994) and S-shaped (B) (Malm, 2006)
634 relationship between exercise and risk of (respiratory) infection