

1 **Abstract**

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

19

20 **Highlights**

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

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

37

38 **Key words**

39 Immunology, Nutrition, Exercise

40

41 **Introduction**

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

47 evaluation of published data, Malm (2006) proposed that elite training is associated with a
48 lower susceptibility to infection compared to high exercise workloads, whereby the relationship
49 between infection risk and training load instead resembles an S-shaped curve (Figure 1)(Malm,
50 2006). Whilst this remains to be verified in prospective studies, it is hypothesised that to
51 maintain elite athlete status there is a pre-requisite to have a robust immune system capable of
52 withstanding infections even during heightened physical and psychological stress. However, it
53 may be that the reduced infection risk in elite athletes observed in previous studies may not
54 reflect a lower impact of physical stress (exercise workload) per se but rather a reflection of
55 better preventive and treatment strategies in place within the studied elite settings.
56 Nevertheless, although elite athletes may not experience a greater annual incidence rate of
57 infections, there is increasing recognition that episodes of upper-respiratory symptoms (URS)
58 typically cluster around intense periods of training (Hellard, Avalos, Guimaraes, Toussaint &
59 Pyne, 2015; Moreira, Delgado, Moreira & Haahtela, 2009; Svendsen, Gleeson, Haugen &
60 Tønnessen, 2015; Svendsen et al., 2016) with a greater risk during winter months (Hellard et
61 al., 2015; Spence et al., 2007).

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

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

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

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

93

94 ***Carbohydrate***

95 It is well documented that carbohydrate intake is a fundamental part of an athlete's diet, both
96 in its ability to enhance physical performance and its role in recovery following exercise.
97 Athletes adopting a train-low compete-high CHO intake approach may increase their risk of
98 immune impairment during periods of restricted CHO intake (Burke, 2010). Previous work has
99 shown that participants on low carbohydrate diets (less than 10% of energy from CHO) for 48
100 – 72 hrs have larger circulating stress hormone (cortisol, adrenaline) and cytokine (IL1ra, IL6,
101 IL10) responses when compared to normal or high CHO diets (Bishop, Walsh, Haines,
102 Richards & Gleeson, 2001b). Whilst it should be noted that it is unusual for elite athletes to
103 regularly have intakes as low as that outlined in the Bishop paper (<10% of daily energy intake
104 from CHO equated to ~1.1 g/kg body mass per day); it is not unheard of for this to be the case
105 for short periods. Athletes may adopt a low CHO intake lasting 1-3 days in specific scenarios
106 e.g. making weight or during periods of tapering where training volume may decrease for
107 competition preparations (Reale, Slater & Burke, 2017). In contrast, high CHO diets have been
108 associated with blunted plasma cortisol responses to exercise due to preservation of plasma
109 glucose, better maintenance of post-exercise plasma glutamine concentrations and attenuated
110 exercise-induced disturbances in the number of circulating leukocytes, neutrophils and
111 lymphocytes (Bishop, Walsh, Haines, Richards & Gleeson, 2001a; Gleeson, Blannin, Walsh,
112 Bishop & Clark, 1998).

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

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

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

138

139 ***Protein***

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

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

158 There has also been interest in single amino acid supplementation to influence immune
159 competence in athletes. Specifically the non-essential amino acid glutamine is an important
160 fuel for immune cells in particular lymphocytes and macrophages (Castell & Newsholme,
161 1997). Endurance exercise can reduce plasma glutamine (Castell & Newsholme, 1998) and it
162 has been hypothesized that oral glutamine supplementation may enhance post-exercise
163 immunity (Castell & Newsholme, 1997). However, the majority of studies have found that
164 reduced plasma glutamine does not meaningfully contribute to exercise-induced immune
165 impairment (Gleeson, 2008). Despite an attractive hypothesis, there is little evidence that
166 glutamine supplementation influences immune responses to exercise.

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

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

171

172 *Hydration*

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

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

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

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

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

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

218

219 *Antioxidants*

220 Strenuous exercise is associated with an acute increase in the production of free radicals
221 (reactive oxygen species (ROS), and reactive nitrogen species (Powers, Nelson & Hudson,
222 2011). An endogenous network of enzymatic (e.g. superoxide dismutase, glutathione
223 peroxidase, catalase) and non-enzymatic antioxidants (e.g. vitamins A, C and E) exist to
224 provide intracellular and extracellular protection against oxidant damage (Powers, Deruisseau,
225 Quindry & Hamilton, 2004). Whilst it is acknowledged these antioxidant defences adapt with
226 training, it has long been debated whether they are sufficient to counter oxidant production
227 during strenuous exercise. Early investigations highlighting the damaging effects of oxidants
228 on muscle and cells led to a proposed role of antioxidant status in exercise-induced immune
229 dysfunction following prolonged exercise (Powers et al., 2011).

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

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

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

264

265 ***Vitamin D***

266 Over the past decade, there has been emerging evidence highlighting the role that vitamin D
267 may have in athlete health (Owens, Fraser & Close, 2015). Commonly known for its role in
268 bone health (Ebeling, 2014) and muscle function (Owens et al., 2015) it is also increasingly
269 recognised for its role in inflammation and aspects of innate and acquired immunity (He et al.,
270 2016).

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

278 Adequate concentration has been previously defined as serum 25 hydroxy vitamin D
279 (25(OH)D) >50 nmol/L by the US Institute of Medicine. However, within the literature, there
280 is a lack of consensus as to what constitutes vitamin D deficiency and what might be classified
281 as an insufficiency for elite athlete health and performance. It is beyond the scope of this review
282 to discuss what constitutes sufficient or optimal circulating concentrations of 25(OH)D, so
283 readers are referred to He et al (2016) for more information (He, Aw Yong, Walsh & Gleeson,
284 2016). The prevalence of deficiency and sufficiency in athletes varies by, training location,
285 sport (Larson-Meyer & Willis, 2010) and skin colour (Pollock, Dijkstra, Chakraverty &
286 Hamilton, 2012), with deficiency being greater in the winter months (Farrokhyar et al., 2015).
287 There is growing evidence that vitamin D likely plays a key role in both innate and acquired
288 immunity through its modulation of gene expression (Kamen & Tangpricha, 2010). Vitamin
289 D upregulates gene expression of antimicrobial peptides, which are important regulators in
290 innate immunity, and downregulate expression of inflammatory cytokines (He et al., 2016).

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

293 A small number of studies have reported negative associations between vitamin D
294 concentration and self-reported URS in athletes (He et al., 2013) and military personnel (Laaksi
295 et al., 2007). In a study of endurance athletes, those in a Vitamin D deficient status group
296 $25(\text{OH})\text{D} < 30\text{nmol/L}$, reported greater number of URS days and higher symptom-severity
297 scores compared to counterparts with greater circulating vitamin D concentrations (He et al.,
298 2013). Elite athletes reporting with URS who had a positive virology/bacteriology result
299 (infectious group) or athletes with a mild to moderate leucocytosis (suggestive group) had
300 significantly lower levels of circulating $25(\text{OH})\text{D}$ levels than athletes with a negative
301 virology/bacteriology count and normal differential leukocyte count (Cox et al., 2008). In a
302 military setting young Finnish conscripts who had low circulating $25(\text{OH})\text{D}$ concentrations
303 (defined by the authors as $<40\text{ nmol/L}$) had significantly more duty days lost to respiratory
304 infection during 6 months of training and were 1.6 times more likely to miss duty due to
305 respiratory infection than those with a circulating $25(\text{OH})\text{D} >40\text{ nmol/L}$ (Laaksi et al., 2007).

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

311

312 ***Bovine colostrum***

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

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

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

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

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

348

349 *Probiotics and Prebiotics*

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

357 It is now recognised that the species composition of the microbiota can be modified by
358 alterations in dietary intake. Regular consumption of probiotic bacteria can positively modify
359 the composition of the gut microbiota and influence immune health (Round & Mazmanian,
360 2009). Alternatively, a prebiotic, a selectively fermented ingredient that allows specific
361 changes, both in the composition and/or activity in the gastrointestinal microbiota can confer
362 benefits upon host well-being and health (Gibson et al., 2017). However, to date there are
363 currently no published studies on the efficacy of prebiotics to reduce URS in athletes. Non-

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

366 A large number of studies have been conducted investigating the effects of probiotics on URS
367 in the non-athlete general population, and readers are referred to the latest Cochrane systematic
368 review for more detail (Hao et al., 2015). The review concluded that probiotics were better than
369 placebo with fewer participants experiencing at least one episode of acute URS, but there was
370 no difference when measuring rate of episodes of URS or the duration of episodes (Hao et al.,
371 2015).

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

379 A randomised crossover trial showed benefit from a daily dose of 1.3×10^{10} colony forming
380 units (CFU) *Lactobacillus fermentum* for 28 days in distance runners during a winter training
381 period (Cox, Pyne, Saunders & Fricker, 2010). The number of days, and severity of self-
382 reported URS was less (~50%) in those receiving the probiotic compared to placebo. This was
383 coupled with a two-fold greater change in whole blood culture interferon- γ with the probiotic;
384 however, there were no changes in salivary IgA, or IL-4 and IL-12 (Cox et al., 2010). Further
385 evidence in support of probiotic feeding showed that 16 weeks of *Lactobacillus casei Shirota*
386 (1.3×10^{11} cells per day) reduced the proportion of active individuals reporting URS by 36%,
387 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*, 2×10^{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 (1.0×10^9 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

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

418 Bartlett, J. D., Hawley, J. A. & Morton, J. P. (2015). Carbohydrate availability and exercise
419 training adaptation: too much of a good thing? *European Journal of Sport Science*, 15(1), 3-
420 12.

421 Bermon, S., Castell, L. M., Calder, P. C., Bishop, N., Blomstrand, E., Mooren, F.
422 C....Senchina, D. S. (2017). Consensus statement immunonutrition and exercise.

423 Berry, D. J., Hesketh, K., Power, C. & Hyppönen, E. (2011). Vitamin D status has a linear
424 association with seasonal infections and lung function in British adults. *British Journal of*
425 *Nutrition*, 106(9), 1433-1440.

426 Bishop, N. C., Walsh, N. P., Haines, D. L., Richards, E. E. & Gleeson, M. (2001a). Pre-
427 exercise carbohydrate status and immune responses to prolonged cycling: I. Effect on
428 neutrophil degranulation. *International Journal of Sport Nutrition and Exercise Metabolism*,
429 11(4), 490-502.

430 Bishop, N. C., Walsh, N. P., Haines, D. L., Richards, E. E. & Gleeson, M. (2001b). Pre-
431 exercise carbohydrate status and immune responses to prolonged cycling: II. Effect on
432 plasma cytokine concentration. *International Journal of Sport Nutrition and Exercise*
433 *Metabolism*, 11(4), 503-512.

434 Burke, L. (2010). Fueling strategies to optimize performance: training high or training low?.
435 *Scandinavian Journal of Medicine & Science in Sports*, 20(s2), 48-58.

436 Castell, L. M. & Newsholme, E. A. (1997). The effects of oral glutamine supplementation on
437 athletes after prolonged, exhaustive exercise. *Nutrition*, 13(7-8), 738-742.

438 Castell, L. M. & Newsholme, E. A. (1998). Glutamine and the effects of exhaustive exercise
439 upon the immune response. *Canadian Journal of Physiology & Pharmacology*, 76(5), 524-
440 532.

441 Cesarone, M. R., Belcaro, G., Di Renzo, A., Dugall, M., Cacchio, M., Ruffini, I...Ledda, A.
442 (2007). Prevention of influenza episodes with colostrum compared with vaccination in
443 healthy and high-risk cardiovascular subjects: the epidemiologic study in San Valentino.
444 *Clinical and Applied Thrombosis/Hemostasis*, 13(2), 130-136.

- 445 Chen, T. C., Chimeh, F., Lu, Z., Mathieu, J., Person, K. S., Zhang, A...Holick, M. F. (2007).
446 Factors that influence the cutaneous synthesis and dietary sources of vitamin D. *Archives of*
447 *Biochemistry & Biophysics*, 460(2), 213-217.
- 448 Cox, A. J., Gleeson, M., Pyne, D. B., Callister, R., Hopkins, W. G. & Fricker, P. A. (2008).
449 Clinical and laboratory evaluation of upper respiratory symptoms in elite athletes. *Clinical*
450 *Journal of Sports Medicine*, 18(5), 438-445.
- 451 Cox, A. J., Pyne, D. B., Saunders, P. U. & Fricker, P. A. (2010). Oral administration of the
452 probiotic *Lactobacillus fermentum* VRI-003 and mucosal immunity in endurance athletes.
453 *British Journal of Sports Medicine*, 44(4), 222-226.
- 454 Davison, G., Kehaya, C., Diment, B. C. & Walsh, N. P. (2016). Carbohydrate
455 supplementation does not blunt the prolonged exercise-induced reduction of in vivo
456 immunity. *European Journal of Nutrition*, 55(4), 1583-1593.
- 457 Davison, G. (2012). Bovine colostrum and immune function after exercise. *Medicine & Sport*
458 *Science*, 59, 62-69.
- 459 Ebeling, P. R. (2014). Vitamin D and bone health: epidemiologic studies. *BoneKEy reports*,
460 3.
- 461 Farrokhyar, F., Tabasinejad, R., Dao, D., Peterson, D., Ayeni, O. R., Hadioonzadeh, R. &
462 Bhandari, M. (2015). Prevalence of vitamin D inadequacy in athletes: a systematic-review
463 and meta-analysis. *Sports Medicine*, 45(3), 365-378.
- 464 Fortes, M. B., Diment, B. C., Di Felice, U. & Walsh, N. P. (2012). Dehydration decreases
465 saliva antimicrobial proteins important for mucosal immunity. *Applied Physiology, Nutrition,*
466 *and Metabolism*, 37(5), 850-859.
- 467 Gibson, G. R., Hutkins, R., Sanders, M. E., Prescott, S. L., Reimer, R. A., Salminen, S.
468 J...Cani, P. D. (2017). Expert consensus document: The International Scientific Association
469 for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of
470 prebiotics. *Nature Reviews Gastroenterology & Hepatology*.
- 471 Gleeson, M., Bishop, N. C., Oliveira, M., McCauley, T., Tauler, P. & Lawrence, C. (2012).
472 Effects of a *Lactobacillus salivarius* probiotic intervention on infection, cold symptom
473 duration and severity, and mucosal immunity in endurance athletes. *International Journal of*
474 *Sport Nutrition and Exercise Metabolism*, 22(4), 235-242.
- 475 Gleeson, M., Bishop, N. C., Oliveira, M. & Tauler, P. (2011). Daily probiotic's
476 (*Lactobacillus casei* Shirota) reduction of infection incidence in athletes. *International*
477 *Journal of Sport Nutrition and Exercise Metabolism*, 21(1), 55-64.
- 478 Gleeson, M., Blannin, A. K., Walsh, N. P., Bishop, N. C. & Clark, A. M. (1998). Effect of
479 low-and high-carbohydrate diets on the plasma glutamine and circulating leukocyte responses
480 to exercise. *International Journal of Sport Nutrition*, 8(1), 49-59.
- 481 Gleeson, M. (2008). Dosing and efficacy of glutamine supplementation in human exercise
482 and sport training. *Journal of Nutrition*, 138(10), 2045S-2049S.

- 483 Green, K. J., Croaker, S. J. & Rowbottom, D. G. (2003). Carbohydrate supplementation and
484 exercise-induced changes in T-lymphocyte function. *Journal of Applied Physiology*, 95(3),
485 1216-1223.
- 486 Hanstock, H. G., Walsh, N. P., Edwards, J. P., Fortes, M. B., Cosby, S. L., Nugent,
487 A...Yong, X. H. A. (2016). Tear fluid SIgA as a noninvasive biomarker of mucosal
488 immunity and common cold risk. *Medicine and Science in Sports & Exercise*, 48(3), 569-
489 577.
- 490 Hao, Q., Dong, B. R. & Wu, T. (2015). Probiotics for preventing acute upper respiratory tract
491 infections. *The Cochrane Library*.
- 492 He, C., Aw Yong, X. H., Walsh, N. P. & Gleeson, M. (2016). Is there an optimal vitamin D
493 status for immunity in athletes and military personnel? *Exercise Immunology Review*, 22:42-
494 64.
- 495 He, C., Fraser, W. D., Tang, J., Brown, K., Renwick, S., Rudland-Thomas, J...Gleeson, M.
496 (2016). The effect of 14 weeks of vitamin D3 supplementation on antimicrobial peptides and
497 proteins in athletes. *Journal of Sports Science*, 34(1), 67-74.
- 498 He, C., Handzlik, M. K., Fraser, W. D., Muhamad, A. S., Preston, H., Richardson, A. &
499 Gleeson, M. (2013). Influence of vitamin D status on respiratory infection incidence and
500 immune function during 4 months of winter training in endurance sport athletes. *Exercise*
501 *Immunology Review*, 19:86-101.
- 502 Hellard, P., Avalos, M., Guimaraes, F., Toussaint, J. F. & Pyne, D. B. (2015). Training-
503 related risk of common illnesses in elite swimmers over a 4-yr period. *Medicine & Science in*
504 *Sports & Exercise.*, 47(4), 698-707.
- 505 Hemilä, H. & Chalker, E. (2013). Vitamin C for preventing and treating the common cold.
506 *The Cochrane Library*.
- 507 Hemila, H. (2013). Vitamin C may alleviate exercise-induced bronchoconstriction: a meta-
508 analysis. *BMJ Open*, 3(6).
- 509 Henson, D., Nieman, D., Parker, J., Rainwater, M., Butterworth, D., Warren, B...Nehlsen-
510 Cannarella, S. (1998). Carbohydrate supplementation and the lymphocyte proliferative
511 response to long endurance running. *International Journal of Sports Medicine*, 19(08), 574-
512 580.
- 513 Jones, A. W., March, D. S., Curtis, F. & Bridle, C. (2016). Bovine colostrum
514 supplementation and upper respiratory symptoms during exercise training: a systematic
515 review and meta-analysis of randomised controlled trials. *BMC sports science, medicine and*
516 *rehabilitation*, 8(1), 21.
- 517 Jones, A., March, D., Thatcher, R., Diment, B., Walsh, N. & Davison, G. (2018). The effects
518 of bovine colostrum supplementation on in vivo immunity following prolonged exercise: a
519 randomised controlled trial. *European Journal of Nutrition*, 1-10.

- 520 Kamen, D. L. & Tangpricha, V. (2010). Vitamin D and molecular actions on the immune
521 system: modulation of innate and autoimmunity. *Journal of Molecular Medicine*, 88(5), 441-
522 450.
- 523 Killer, S. C., Svendsen, I. S. & Gleeson, M. (2015). The influence of hydration status during
524 prolonged endurance exercise on salivary antimicrobial proteins. *European Journal of*
525 *Applied Physiology*, 115(9), 1887-1895.
- 526 Korhonen, H., Marnila, P. & Gill, H. (2000). Bovine milk antibodies for health. *British*
527 *Journal of Nutrition*, 84(S1), 135-146.
- 528 Laaksi, I., Ruohola, J. P., Tuohimaa, P., Auvinen, A., Haataja, R., Pihlajamaki, H. &
529 Ylikomi, T. (2007). An association of serum vitamin D concentrations < 40 nmol/L with
530 acute respiratory tract infection in young Finnish men. *American Journal of Clinical*
531 *Nutrition*, 86(3), 714-717.
- 532 Larson-Meyer, D. E. & Willis, K. S. (2010). Vitamin D and athletes. *Current Sports*
533 *Medicine Reports*, 9(4), 220-226.
- 534 Malm, C. (2006). Susceptibility to infections in elite athletes: the S-curve. *Scandinavian*
535 *Journal of Medicine & Science in Sports*, 16(1), 4-6.
- 536 Maughan, R. & Shirreffs, S. (2004). Exercise in the heat: challenges and opportunities.
537 *Journal of Sports Science*, 22(10), 917-927.
- 538 Mitchell, J. B., Dugas, J. P., McFarlin, B. K. & Nelson, M. J. (2002). Effect of exercise, heat
539 stress, and hydration on immune cell number and function. *Medicine & Science in Sports &*
540 *Exercise*, 34(12), 1941-1950.
- 541 Moreira, A., Delgado, L., Moreira, P. & Haahtela, T. (2009). Does exercise increase the risk
542 of upper respiratory tract infections? *British Medical Bulletin*, 90(1), 111-131.
- 543 Nieman, D. C. (1994). Exercise, upper respiratory tract infection, and the immune system.
544 *Medicine & Science in Sports & Exercise*, 26(2), 128-139.
- 545 Nieman, D. C., Henson, D. A., Fagoaga, O. R., Utter, A. C., Vinci, D. M., Davis, J. M. &
546 Nehlsen-Cannarella, S. (2002). Change in salivary IgA following a competitive marathon
547 race. *International Journal of Sports Medicine*, 23(01), 69-75.
- 548 Nieman, D. C. & Mitmesser, S. H. (2017). Potential Impact of Nutrition on Immune System
549 Recovery from Heavy Exertion: A Metabolomics Perspective. *Nutrients*, 9(5), 513.
- 550 Nieman, D. C., Henson, D. A., McAnulty, S. R., McAnulty, L., Swick, N. S., Utter, A.
551 C...Morrow, J. D. (2002). Influence of vitamin C supplementation on oxidative and immune
552 changes after an ultramarathon. *Journal of Applied Physiology*, 92(5), 1970-1977.
- 553 Ontsouka, C., Bruckmaier, R. & Blum, J. (2003). Fractionized milk composition during
554 removal of colostrum and mature milk. *Journal of Dairy Science*, 86(6), 2005-2011.

- 555 Owens, D. J., Fraser, W. D. & Close, G. L. (2015). Vitamin D and the athlete: emerging
556 insights. *European Journal of Sport Science*, 15(1), 73-84.
- 557 Owens, D. J., Sharples, A. P., Polydorou, I., Alwan, N., Donovan, T., Tang, J....Close, G. L.
558 (2015). A systems-based investigation into vitamin D and skeletal muscle repair,
559 regeneration, and hypertrophy. *American Journal of Physiology-Endocrinology &
560 Metabolism*, 309(12), E1019-31.
- 561 Patiroğlu, T. & Kondolot, M. (2013). The effect of bovine colostrum on viral upper
562 respiratory tract infections in children with immunoglobulin A deficiency. *The Clinical
563 Respiratory Journal*, 7(1), 21-26.
- 564 Pollock, N., Dijkstra, P., Chakraverty, R. & Hamilton, B. (2012). Low 25 (OH) vitamin D
565 concentrations in international UK track and field athletes. *South African Journal of Sports
566 Medicine*, 24(2).
- 567 Powers, S. K., Deruisseau, K. C., Quindry, J. & Hamilton, K. L. (2004). Dietary antioxidants
568 and exercise. *Journal of Sports Science*, 22(1), 81-94.
- 569 Powers, S. K., Nelson, W. B. & Hudson, M. B. (2011). Exercise-induced oxidative stress in
570 humans: cause and consequences. *Free Radical Biology and Medicine*, 51(5), 942-950.
- 571 Pyne, D. B., West, N. P., Cox, A. J. & Cripps, A. W. (2015). Probiotics supplementation for
572 athletes—Clinical and physiological effects. *European Journal of Sport Science*, 15(1), 63-72.
- 573 Reale, R., Slater, G. & Burke, L. M. (2017). Acute-weight-loss strategies for combat sports
574 and applications to Olympic success. *International Journal of Sports Physiology and
575 Performance*, 12(2), 142-151.
- 576 Round, J. L. & Mazmanian, S. K. (2009). The gut microbiota shapes intestinal immune
577 responses during health and disease. *Nature Reviews Immunology*, 9(5), 313-323.
- 578 Sawka, M. N. & Coyle, E. F. (1999). Influence of body water and blood volume on
579 thermoregulation and exercise performance in the heat. *Exercise & Sport Science Reviews*,
580 27, 167-218.
- 581 Shing, C. M., Peake, J. M., Suzuki, K., Jenkins, D. G. & Coombes, J. S. (2013). A pilot
582 study: bovine colostrum supplementation and hormonal and autonomic responses to
583 competitive cycling. *Journal of Sports Medicine & Physical Fitness*, 53(5), 490-501.
- 584 Somerville, V. S., Braakhuis, A. J. & Hopkins, W. G. (2016). Effect of Flavonoids on Upper
585 Respiratory Tract Infections and Immune Function: A Systematic Review and Meta-
586 Analysis. *Advance in Nutrition*, 7(3), 488-497. doi:10.3945/an.115.010538 [doi].
- 587 Spence, L., Brown, W. J., Pyne, D. B., Nissen, M. D., Sloots, T. P., McCormack, J.
588 G....Fricker, P. A. (2007). Incidence, etiology, and symptomatology of upper respiratory
589 illness in elite athletes. *Medicine & Science in Sports & Exercise*, 39(4), 577-586.

590 Svendsen, I. S., Gleeson, M., Haugen, T. A. & Tønnessen, E. (2015). Effect of an intense
591 period of competition on race performance and self-reported illness in elite cross-country
592 skiers. *Scandinavian Journal of Medicine & Science in Sports*, 25(6), 846-853.

593 Svendsen, I. S., Killer, S. C. & Gleeson, M. (2014). Influence of hydration status on changes
594 in plasma cortisol, leukocytes, and antigen-stimulated cytokine production by whole blood
595 culture following prolonged exercise. *ISRN nutrition*, 2014.

596 Svendsen, I. S., Taylor, I. M., Tønnessen, E., Bahr, R. & Gleeson, M. (2016). Training-
597 related and competition-related risk factors for respiratory tract and gastrointestinal infections
598 in elite cross-country skiers. *British Journal of Sports Medicine*, 50(13), 809-815.

599 Tarnopolsky, M. (2004). Protein requirements for endurance athletes. *Nutrition*, 20(7), 662-
600 668.

601 Uruakpa, F., Ismond, M. & Akobundu, E. (2002). Colostrum and its benefits: a review.
602 *Nutrition Research*, 22(6), 755-767.

603 Von Essen, M. R., Kongsbak, M., Schjerling, P., Olgaard, K., Ødum, N. & Geisler, C.
604 (2010). Vitamin D controls T cell antigen receptor signaling and activation of human T cells.
605 *Nature Immunology*, 11(4), 344-349.

606 Wall, B. A., Watson, G., Peiffer, J. J., Abbiss, C. R., Siegel, R. & Laursen, P. B. (2015).
607 Current hydration guidelines are erroneous: dehydration does not impair exercise
608 performance in the heat. *British Journal of Sports Medicine*, 49(16), 1077-1083.

609 Webb, A. R., Kline, L. & Holick, M. F. (1988). Influence of season and latitude on the
610 cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will
611 not promote vitamin D3 synthesis in human skin. *The Journal of Clinical Endocrinology &
612 Metabolism*, 67(2), 373-378.

613 West, N. P., Pyne, D. B., Cripps, A. W., Hopkins, W. G., Eskesen, D. C., Jairath,
614 A...Fricker, P. A. (2011). Lactobacillus fermentum (PCC®) supplementation and
615 gastrointestinal and respiratory-tract illness symptoms: a randomised control trial in athletes.
616 *Nutrition Journal*, 10(1), 30.

617 Williams, N. C., Johnson, M. A., Shaw, D. E., Spendlove, I., Vulevic, J., Sharpe, G. R. &
618 Hunter, K. A. (2016). A prebiotic galactooligosaccharide mixture reduces severity of
619 hyperpnoea-induced bronchoconstriction and markers of airway inflammation. *British
620 Journal of Nutrition*, 116(5), 798-804.

621 Witard, O. C., Turner, J. E., Jackman, S. R., Kies, A. K., Jeukendrup, A. E., Bosch, J. A. &
622 Tipton, K. D. (2014). High dietary protein restores overreaching induced impairments in
623 leukocyte trafficking and reduces the incidence of upper respiratory tract infection in elite
624 cyclists. *Brain Behaviour & Immunology*, 39, 211-219.

625 Wylie, K. M., Truty, R. M., Sharpton, T. J., Mihindukulasuriya, K. A., Zhou, Y., Gao,
626 H...Pollard, K. S. (2012). Novel bacterial taxa in the human microbiome. *PloS one*, 7(6),
627 e35294.

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	[✓]	[✓]	[✱]	<p>●●●●●</p> <p>Lack of RCTs investigating effect on URS</p>	<p>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</p>	<p>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.</p> <p>These intakes may attenuate the rise in stress hormones and indirectly limit the degree of exercise-induced immune impairment.</p> <p>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.</p>
PROTEIN/AMINO ACIDS	[✓]	[✓]	[✱]	<p>◎●●●●</p> <p>Limited number of RCTs showing benefit of additional total protein or glutamine supplementation.</p>	<p>Further RCTs to establish if additional total protein or glutamine supplementation impacts on URS and integrated in vivo measures of immune function</p>	<p>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.</p> <p>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</p>

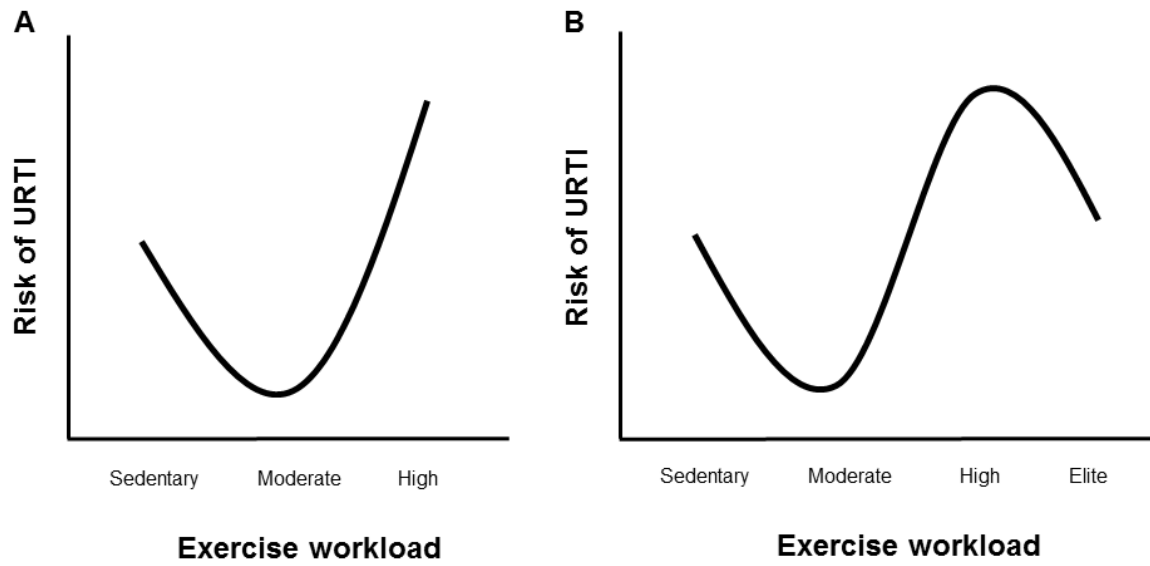
						<p>day is recommended for maximising net protein balance.</p> <p>Further supplementation of protein intake or single/multiple amino acids is not recommended to improve immunity and reduce URS incidence.</p>
HYDRATION	[✓]	[?]	[*]	<p>○○○○○</p> <p>Lack of RCTs investigating effect on URS</p>	<p>Lack of 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.</p>	<p>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.</p> <p>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.</p>
ANTIOXIDANT SUPPLEMENTATION	[✓]	[✓]	[*]	<p>◎◎◎○○</p> <p>Meta-analysis of RCTs of heavy acute exercise (and/cold) stress</p>	<p>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.</p>	<p>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.</p> <p>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.</p>
VITAMIN D SUPPLEMENTATION	[✓]	[✓]	[*]	<p>◎◎◎○○</p>	<p>RCTs of vitamin D supplementation (to correct deficiency) to establish</p>	<p>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,</p>

				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	<p>although considerations must be made for latitude and skin type.</p> <p>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.</p> <p>In the absence of deficiencies, most athletes are recommended to avoid excessive intake of vitamin D.</p>
BOVINE COLOSTRUM	[✓]	[✓]	[✓]	⊙⊙⊙⊙⊙ Meta-analyses of RCTs in athlete populations	<p>Low precision of estimates of effect on URS need to be followed up with appropriately designed and adequately powered RCTs.</p> <p>Key mechanisms of action need to be elucidated.</p>	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	[✓]	[✓]	[?]	⊙⊙⊙⊙⊙ 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 1×10^9 CFU per day should be considered to ensure the greatest survival to the gut, and subsequent immune modulation.
--	--	--	--	----------------------------	---	--

630

631



632

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