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1 **There is limited existing evidence to support the common assumption that strenuous**
2 **endurance exercise bouts impair immune competency**

3

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13

14

15 **Key words:** Exercise, Physical activity, Endurance sports, Over-training, Upper respiratory
16 tract infections, Open window hypothesis, Infection susceptibility, Immune competency,
17 Immuno-suppression, Immuno-depression

18

19 **Introduction**

20

21 Research from the 1980s and 1990s led to three principles of exercise immunology being
22 formed which imply that an acute bout of moderate-to-vigorous intensity endurance exercise
23 can induce a short-term period of immuno-suppression. This prevailing dogma has been
24 challenged recently [1]. Following acute bouts of exercise, particularly endurance activities,
25 such as running for several hours, it has generally been accepted that; (i) infection risk is
26 increased; (ii) salivary IgA temporarily declines; and (iii) transient decreases in the number
27 and function of immune cells in blood represents immuno-suppression. These observations led
28 to the ‘open-window hypothesis’ which purports that the immune system can be transiently
29 compromised after some forms of acute exercise. In this editorial, we briefly summarise key
30 messages from a recent narrative review that challenges these conclusions [1]. Our focus herein
31 is on the immunological effects of moderate-to-vigorous intensity endurance exercise bouts.
32 Other forms of exercise, such as strengthening or resistance exercise, are beyond the scope of
33 this editorial. Overall, we state that there is limited robust evidence to support an immuno-

34 suppressive effect of any exercise form. We highlight that further research is required to fully
35 understand the immunological effects of endurance exercise training that is particularly
36 prolonged (i.e. at least several hours) regular (i.e. once or twice a day) demanding (i.e.
37 moderate-to-vigorous intensity) and chronic (i.e. performed over weeks or months). In
38 summary, the belief that forms of exercise can be immuno-suppressive is counterproductive
39 for encouraging exercise as a preventative and therapeutic strategy for chronic disease. Indeed,
40 we advocate research that examines the *benefits* of exercise for immune competency, and
41 briefly highlight areas that could be prioritised.

42

43 **Exercise and infections**

44

45 Well known studies from the 1980s and 1990s reported that infectious episodes are increased
46 after taking part in mass participation endurance sport events. For example, one third of
47 participants in the 1982 Two Oceans 56 km ultra-marathon in Cape Town South Africa, self-
48 reported symptoms of upper respiratory tract infections within two weeks of the race [2]. The
49 age-matched control group, who shared a home with another of the race competitors, reported
50 half the symptoms in the same period [2]. It should be considered however, that attending any
51 mass participation event – whether exercising or not – is likely to increase the risk of
52 encountering pathogens due to crowds of people. For example, a study has shown that around
53 one third of people attending a mass-participation religious gathering reported infections, and
54 symptom reporting was most common among individuals with the greatest exposure to crowds
55 [3]. Similarly, it is often claimed that athlete populations exhibit a high frequency of illness
56 symptoms. However, evidence shows that athletes exhibit a similar number of illness episodes
57 as the general population annually, but their symptoms often cluster around winter months,
58 sometimes during concentrated periods of training or when attending competition events [1].

59

60 A limitation of most studies interpreting self-reported illness symptoms is that potential
61 infections were not confirmed by laboratory analysis. Indeed, a study of athletes reporting
62 illness symptoms over five-months, used nasopharyngeal and throat swabs to show that only
63 one third of self-diagnoses represented genuine infections [4]. Thus, most symptoms reported
64 by athletes are likely to be caused by allergy, asthma or non-specific mucosal inflammation
65 rather than pathogens and exercise-induced immuno-suppression [5]. Among the few genuine
66 infections, if there is an immunological component of risk, then non-exercise factors most
67 likely contribute. These can include long-haul air travel crossing multiple time-zones, exposure

68 to hypobaric hypoxia, radiation, temperature changes, sleep disruption, altered diet,
69 dehydration and psychological stress [5, 6].

70

71 **Exercise and salivary IgA**

72

73 Studies are often cited showing that salivary IgA, measured as absolute concentration (mg/mL)
74 or as secretion rate (IgA protein concentration multiplied by saliva flow rate; mg/mL/min) can
75 decline by 20-25% following exercise bouts [1]. Yet, other studies, which are cited less, have
76 shown the opposite effect [7]. Although resting levels of salivary IgA have been linked to self-
77 reported illness symptoms, transient fluctuations and inter-individual differences could be
78 driven by factors such as circadian rhythm, psychological stress, dehydration, diet, ethnicity,
79 medications, biological sex, and phase of the menstrual cycle. Perhaps most importantly, given
80 that periodontal disease is common among athletes [8], oral health status results in profound
81 between-person salivary IgA variation [9] but is rarely considered. Measuring salivary IgA in
82 isolation provides an incomplete and potentially confusing assessment of immune competency.

83

84 Recent studies have expanded salivary analyses to include several other anti-microbial proteins
85 or peptides (e.g. alpha-amylase, human neutrophil peptides 1-3, human defensins 5-6,
86 lactoferrin, LL-37, and lysozyme) characterising fluctuations in response to exercise [10].
87 However, many more proteins require exploration and validation as predictors of infection risk.
88 For example, 151 differentially expressed proteins were identified when examining nasal
89 mucosal washes from people infected with influenza compared to uninfected controls using a
90 proteomic approach that quantified around 1000 proteins [11]. Many aspects of both cellular
91 and humoral mucosal immunity have been examined as predictors of infections. Although
92 salivary IgA has received most attention, it is likely that relationships between illness
93 symptoms and most measurements of mucosal immunity are influenced by other factors [12].
94 Between-person differences in infection susceptibility – aside from the influence of pathogen
95 exposure, environmental and behavioural factors – are most likely explained by single
96 nucleotide polymorphisms in key genes leading to individual idiosyncrasies in multiple aspects
97 of immune function.

98

99 **Exercise and changes to immune cell frequency and functional capacity**

100

101 During exercise, immune cell frequency in blood is increased [13]. Some cells detach from the
102 endothelium and recirculate due to changes in shear forces, blood pressure, and sympathetic
103 nervous system activity, whereas other cells mobilise from tissues such as the spleen. Upon
104 exercise cessation, and most prominently among lymphocytes, cell frequency falls below
105 resting levels to a nadir 1 or 2 hours later, usually returning to baseline within 24 hours. These
106 post-exercise changes are partly due to the functional properties of the mobilised cells but also
107 due to hypothalamic-pituitary-adrenal axis activation. Coinciding with changes in cell
108 frequency, parallel alterations to cell function have been reported (e.g. cytokine production,
109 proliferation, migration capability, cytotoxicity) typically characterised by increases during
110 exercise, and decreases after, leading to speculation that immune function is transiently
111 compromised [14].

112

113 A more contemporary viewpoint is that these observations, particularly among lymphocytes,
114 are part of a well-orchestrated immune-surveillance response. Exercise redeploys highly
115 functional sub-populations of T cells, B cells and Natural Killer cells to peripheral tissues (e.g.
116 mucosal surfaces) to identify and eradicate infected cells and damaged or malignant cells;
117 termed the acute-stress/exercise immune-enhancement hypothesis [15]. Pivotal research by
118 Kruger and colleagues, using fluorescent cell tracking in rodents, showed that T cells are
119 redeployed to the gut, lungs, and bone marrow following exercise [16] reflecting heightened
120 immune-surveillance at sites where pathogens are likely to be encountered (gut, lungs) and
121 heightened immuno-regulatory activities (in bone marrow). In addition, 24 hours after exercise,
122 a small number of apoptotic lymphocytes accumulate in bone marrow and blood coinciding
123 with a mobilisation of haematopoietic stem cells [17]. Further, injecting apoptotic lymphocytes
124 (or their supernatant) into the bloodstream stimulates haematopoietic stem cell mobilisation
125 within 2 hours [17]. These observations support the proposal that exercise reverses T cell
126 immunosenescence by “making immunological space” [18]. In this hypothesis, it is proposed
127 that exercise mobilises senescent T cells into blood, which home to tissues where some undergo
128 apoptosis. Naïve T cells refill the “immunological space” that has been created, due to exercise-
129 induced thymopoiesis or extrathymic development, perhaps in response to IL-7 released from
130 contracting skeletal muscle [18, 19].

131

132 Although cell frequency in blood is informative, cell function is arguably more clinically
133 relevant, but is strongly influenced by the number and type of cells assessed. During exercise,
134 blood is predominantly occupied by cells capable of responding strongly to *in vitro* stimuli,

135 and therefore many studies have reported “improved” function of cells close to an exercise
136 stimulus. In the hours following exercise, due to redeployment of highly functional cells to
137 tissues, blood has fewer cells capable of responding to *in vitro* stimuli, explaining the
138 commonly reported “decrease” in cell function post-exercise. Lancaster and colleagues
139 demonstrated these effects in 2005, reporting that interferon-gamma production by stimulated
140 CD8+ T cells is reduced 2 hours after moderate-intensity cycling for 2.5 hours [20].
141 Importantly, the reduced capacity to produce interferon-gamma was due to fewer interferon-
142 gamma positive CD8+ T cells in blood at the time of sampling [20]. Adequate resolution can
143 only be achieved by examining cell function on a per-cell and per-phenotype basis while
144 considering the kinetics of cell sub-populations and their proportions in the samples assessed.
145 For example, it has been shown that the frequency of CD8+ T cells producing cytokines is
146 dependent on the proportion of naïve and memory cell sub-populations within the T cell pool,
147 differentiated by CD27 and CD45RA [21].

148

149 These principles, although less widely investigated, also likely apply to cells of the innate
150 immune system. For example, changes to neutrophil function with exercise might represent a
151 shift in the proportion of immature and mature cells, and the concomitant migratory or homing
152 capability of cells might therefore explain differences in cell function especially if reported
153 between different biological fluids and tissues [22]. There has been an over-generalisation that
154 “impaired” function of adaptive immune cells following exercise – which, as explained above,
155 is influenced by individual cell properties and their proportions present in samples assayed –
156 also applies to cells of the innate immune system. Indeed, some reports are often overlooked,
157 showing that innate immune cells, such as macrophages and neutrophils, exhibit *increased* cell
158 functions (e.g. chemotaxis, phagocytosis and microbicidal capacity) following exercise [23,
159 24]. Thus, results of studies examining exercise-induced changes to cell frequency and function
160 must be interpreted carefully considering differential effects on innate or adaptive immune
161 cells, their sub-populations, and the time-dependent changes in the cellular composition of
162 blood.

163

164 **Neuroendocrine regulation of immune cell function**

165

166 The catecholamines adrenaline and noradrenaline – a focus for some mechanistic
167 investigations of exercise and immune cell function – are often labelled as “immuno-
168 suppressors”, which is an oversimplification [23, 24]. Conclusions have predominantly been

169 made with unfractionated lymphocytes, or CD4⁺ T cells isolated at rest, manipulating
170 catecholamine exposure during proliferative stimulation using mitogens such as
171 phytohaemagglutinin (PHA). There are, however, important nuances when interpreting *in vitro*
172 experiments and extrapolating findings to *in vivo* processes, even at rest. First, the anti-
173 proliferative effects of noradrenaline reported at high concentrations do not always occur with
174 lower levels of noradrenaline, especially in the presence of glucocorticoids [23]. Instead,
175 reports show these conditions can *stimulate*, rather than suppress, lymphocyte proliferation and
176 are perhaps more representative of *in vivo* settings [23]. Indeed, although glucocorticoids are
177 considered immunosuppressive, the exercise-induced cortisol response stimulates innate and
178 adaptive immune cells to migrate out of the circulation for tissue immune-surveillance [25,
179 26]. Second, the suppressive effect that catecholamines can have on lymphocyte proliferation
180 do not generalise to all cells. For example, catecholamines can *stimulate* macrophage and
181 neutrophil function [23, 24] and there is further complexity when examining cell sub-
182 populations. Experiments assessing adrenergic stimulation of Natural Killer cells, CD4⁺ and
183 CD8⁺ T cells, and antigen presenting cells support a suppressive effect [27] but more resolution
184 is provided by separating CD8⁺ T cells into naïve and memory sub-populations [28]. These
185 results show differential effects of noradrenaline, which *stimulates* inflammatory cytokine
186 production and *tempers* activation-induced proliferation in memory cells, but exerts minimal
187 effects in naïve cells [28]. The complexities of *in vitro* results are amplified with *in vivo* studies,
188 especially in an exercise context, and further investigations are required. However, we
189 emphasise it is an oversimplification to conclude that forms of exercise, which stimulate a
190 neuroendocrine response, suppress immune cell function and impair overall immune
191 competency.

192

193 **Questions that remain unanswered: future research for examining exercise, immune** 194 **function and infection susceptibility**

195

196 Epidemiological associations between exercise volume and infection risk – usually assessed
197 via self-reported illness symptoms – are often described as a ‘J-shaped curve’ [29]. This
198 relationship infers that people accumulating large volumes of exercise exhibit a greater
199 infection risk than those who do not exercise, and compared to individuals who exercise at
200 moderate levels, which is protective, the risk of infections is even greater [29]. However, the
201 immunological effects of undertaking exceptionally large volumes of long-duration endurance
202 exercise training, particularly when accumulated over weeks and months, are not well

203 understood. Circadian secretion profiles and overall exposure to various biochemical and
204 neuroendocrine factors may be altered, and these changes could in principle, affect aspects of
205 immune function [30]. In addition, given the rapidly developing field of immuno-metabolism,
206 we anticipate metabolic investigations of immune cell function in an exercise context, and a
207 renewed search for factors that are depleted (or accumulate) following individual or
208 accumulated bouts of exercise. Although some factors have previously been discounted (e.g.
209 the amino acid glutamine; [31]), and, extreme metabolic disruption via starvation has relatively
210 modest effects on immune function [32], improvements in technology and immuno-metabolic
211 understanding may yield further insights, especially in studies that tease apart complex
212 interactions between exercise, nutrition, and immune competency. However, as with
213 assessments of immune cell function, it is critical that immuno-metabolic measurements are
214 examined on a per-cell and per-phenotype basis, considering the time-dependent influence
215 exercise has on the cellular composition of blood. Potential biomarkers of immune
216 competency, or processes that appear to be affected by exercise, should subsequently be
217 validated against infections that have been confirmed with laboratory diagnostics.

218

219 Exercise-induced leukocytosis is one of the most reproduced findings in exercise physiology,
220 and we anticipate future studies will continue to replicate classical findings with emerging
221 forms of popular exercise. A recent example is sprint-interval exercise, also referred to as High
222 Intensity Interval Exercise (HIIE), which, as might be expected, stimulates T cell and Natural
223 Killer cell trafficking, but responses are larger following a continuous and sustained exercise
224 stimulus [33]. Other studies have shown that frequent HIIE (or High Intensity Interval
225 Training; HIIT) does not compromise mucosal immunity [34] and that both HIIT and
226 continuous training similarly improve innate immune cell function at rest [35]. Exploring the
227 immunological effects of different exercise modes has merit for improving understanding of
228 immune function, especially if the optimal mode of exercise is yet to be established for
229 particular groups (e.g. patients with chronic disease).

230

231 **Conclusion: exercise in general is beneficial for immune competency across the lifespan**
232 **in health and disease**

233

234 In summary, based on current evidence, it is misleading to state that *any* form of exercise is
235 immuno-suppressive. This belief is counterproductive for encouraging exercise as a
236 preventative and therapeutic strategy for chronic disease. Indeed, we encourage research that

237 examines exercise-induced *enhancement* of immune competency, which could be particularly
238 beneficial for elderly people and patients with diseases that have an immunological aetiology.
239 For example, the acute immune response to single exercise bouts, and chronic adaptation with
240 regular endurance exercise training, both bolster immune responses to vaccination in younger
241 and older people [36]. When forms of exercise are prescribed to reduce cancer risk or to
242 facilitate cancer therapy, there are likely to be multiple mechanisms, and some are probably
243 immunological. These mechanisms might elicit their effects via the transitory responses to
244 acute exercise bouts, the cumulative effects of repeated transitory responses, or the long-term
245 chronic adaptation with exercise training. However, in settings where tumour cells have
246 developed – or are perhaps developing – a strong emphasis has been placed on the effects that
247 individual bouts of exercise can have. For example, acute moderate-to-vigorous intensity
248 endurance exercise stimulates Natural Killer cells to detect and eliminate tumours (or pre-
249 cancer cells) [37]. In addition, serum collected immediately after acute endurance exercise
250 bouts has been shown to impair breast cancer cell viability, but serum collected at rest after
251 long-term endurance training had no effects [38]. Finally, being regularly active, partly by
252 engaging in forms of exercise, might limit or delay ageing of the immune system, potentially
253 reducing the chance of developing infections and cancer [39, 40].

254

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463 **the life-course limits ageing of the immune system.**
464
- 465 40. Turner JE, Brum PC. Does regular exercise counter T cell immunosenescence reducing
466 the risk of developing cancer and promoting successful treatment of malignancies?
467 *Oxid Med Cell Longev.* 2017;2017:4234765.
468
- 469 **** A comprehensive review article which explores whether exercise reduces the risk of**
470 **developing cancer by limiting ageing of the immune system.**
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