# *Paediatric Exercise Immunology: Health and Clinical Applications*

**Running Title: Paediatric Exercise Immunology**

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## Abstract

*Considerable advances have been made in exercise immunology over the last two decades, and it is becoming evident that many of the health benefits of regular physical activity may be directly related to activation of the immune system. The number of investigations devoted to the paediatric population, however, remains low, and our understanding of the interaction between acute and chronic exercise and the immune system in youth is, therefore, relatively deficient. The purpose of this review is to disseminate the existing knowledge in the area of paediatric exercise immunology and to discuss growth-related issues with respect to exercise and the immune system in health and disease. In general, healthy children experience smaller overall perturbations to the immune system in response to an acute bout of exercise, and demonstrate a faster recovery of the immune system following exercise. The immune effects of chronic exercise and/or exercise training in healthy children and adolescents have not been well-documented, and there is only limited evidence to suggest that moderate to high levels of habitual physical activity are associated with a reduction in the incidence of infection and illness in youth. A number of paediatric clinical conditions expressing a strong immune component are also discussed in the context of acute exercise effects and the potential benefits of enhanced physical activity. Given the linkage between childhood health and adult disease, paediatric exercise immunology represents a fruitful area for future study.*

**Keywords:** Youth, Growth, Immune system, Physical activity

## Introduction

Exercise scientists have been investigating, for some time, how acute and chronic exercise might influence the immune system's ability to combat infection and illness. Despite the proliferation of this field, however, there remains a paucity of studies devoted to the paediatric population. Consequently, very little

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is known regarding the interactions of acute and chronic exercise and the immune system in children and adolescents and their implications for health and disease. Moreover, advice regarding exercise and infection offered to the young athlete must be based on adult data, which may not be accurate or even appropriate for the child. On the one hand, this lack of literature is not surprising given the ethical issues associated with blood collection in younger individuals and the simple fact that few laboratories in the world are interested in paediatric exercise science. On the other hand, it is somewhat surprising that more investigations have not been conducted when one considers the well-documented age-related changes in the immune system throughout childhood (e.g., 11,12,41,42), suggesting that there may also be growth-related changes in the immune response to exercise. An improved understanding of "normal" immunological responses to acute exercise in healthy children and adolescents is also of clinical significance. What is a safe exercise prescription for children with, or recovering from, an immune-related disease? How do we distinguish normal exercise-induced changes in a child's immune system from abnormal changes? What interventions, nutritional or otherwise, can or should be incorporated into the prescription of exercise to promote immune health in growing children? Answers to these practical questions are important to the paediatric health professional. It is also unclear whether regular exercise during childhood is protective against infection and illness, as has been suggested for adults (74). Moreover, the immune system is intimately linked to health disorders such as obesity, Type 2 diabetes mellitus (T2DM), and cardiovascular disease. In today's society, physical *inactivity* among children and adolescents is a serious problem and is strongly associated with high rates of obesity (184) and a parallel occurrence of "adult-type" health problems such as T2DM (136,157) and vascular dysfunction (137,195). To what extent the early onset of these adult-type disorders during childhood is linked to development of the immune system is unknown. That regular exercise during childhood may influence normal growth and development of the immune system, and thus aetiology of adult disease, is, therefore, of considerable interest.

To address some of the above issues, this review will focus on the exercise immunology literature that pertains to children and adolescents, with special attention given to potential child-adult differences. To accomplish this objective, a primary literature search was performed in the PubMed and Sport discus databases using various keyword combinations (e.g., "exercise" AND "children" AND "immune"). The reference list in a retrieved article and personal files provided additional literature. While every effort was made to retrieve all available literature, it is not impossible that some contributions (perhaps in another language) may have been missed. Given the infancy of paediatric exercise immunology as a discipline, it was decided not to utilise a systematic review approach, but to include all relevant papers looking at exercise, immune function and children. Accordingly, the primary objective of this paper is to provide an evaluation of existing knowledge in the area and, where appropriate, to provide original data and new observations that supplement this aim. This paper will also briefly address exercise immunology literature regarding specific clinical paediatric conditions, which express a strong immune component, and it is organized under the following headings:

- Historical perspectives
- Growth and development of the immune system
- Effects of acute exercise on the immune system
- Effects of chronic exercise on the immune system
- Physical activity and risk of infection
- Infection and illness in the young athlete
- Exercise and the immune system in paediatric clinical conditions

## Historical perspectives

Exercise immunology, as a scientific discipline, has its roots in data collected more than 100 years ago. A considerable amount of literature reviewed in the 1930s (61,101,166) described variations in leukocyte counts in response to physical activity and training, and in a 1935 review of the literature, Garrey and Bryan (61) noted an 1893 publication by Schulz. More recently, interest in exercise immunology was driven primarily by anecdotal evidence from athletes and coaches indicating that periods of intense training were associated with an increased frequency of illness and infection. The early 1990s were characterised by an exponential increase in the number of papers devoted to exercise immunology (123). Today, molecular approaches are being applied to the study of exercise immunology, including intracellular pathways leading to cellular activation (e.g., 107) and the expression of genes and gene products (e.g., 30,203). Such advances are sure to add further credibility to the field of exercise immunology.

But what about the paediatric angle? From a historical perspective and to the best of this author's knowledge, the earliest published data (in English) reporting a leukocytosis of physical activity in children appear to be those of Christensen and Rothstein (27) published in 1979. In a way, this study was the first to determine the effect of exercise intensity on immune changes, by comparing the total leukocytosis and neutrophilia in newborn babies in response to three conditions: circumcision, chest physical therapy, and heel puncture. The most robust increases in circulating total leukocyte (~46%) and neutrophil (~48%) counts were observed following the "most violent physical activity" (i.e., circumcision), with a full recovery of cell counts to resting levels by 60 min following the procedure (27). Later in 1987, the same authors documented exercise-induced changes in blood leukocyte subsets in teenage athletes (26). Since that time, the number of publications devoted to children and adolescents has grown, but remains relatively low in relation to an estimate of the total number of studies published in the field (Figure 1). In this regard, paediatric exercise immunology is a relatively new development.

## Growth and development of the immune system

### Overview

A *brief* introduction to the effects of chronological and biological (i.e., pubertal) age and sex on the immune system under resting conditions is essential to provide a framework against which to evaluate the effects of exercise on the immune system during growth. Indeed, the immune system does not remain static across the lifespan, and age-related changes during childhood and adolescence have been

studied for more than 60 years (86). An exhaustive examination of the available literature, however, is far beyond the scope of this paper.

**Changes with chronological age**

Mucosal immunity, and salivary immunoglobulin A (sIgA) in particular, gradually increases during the first decade of life (35,36). Like other aspects of immunity, however, mucosal development is under numerous control factors (e.g., environmental) (64). In terms of the cellular immune system, the total leukocyte count consistently decreases throughout childhood (48,77,78,82,151,152,199). The total peripheral lymphocyte pool also decreases during childhood (48,78, 82, 151, 152, 199), but to a greater degree. While the absolute lymphocyte count decreases during childhood, the relative proportions of various lymphocyte subsets may increase, decrease or remain stable. The proportion of $CD4^+$ cells, for example, has been shown to either decrease (77, 129, 142, 199) or remain stable (48, 82, 151, 152), whereas the proportion of $CD8^+$ cells has been shown to either increase (129,151,152,199) or remain stable (48, 77, 82, 142) with age. In light of the unidirectional change in the total lymphocyte pool, the absolute $CD4^+$ cell count usually decreases gradually with age, but the $CD8^+$ cell count may remain constant, thus highlighting the cautious interpretation required when only relative values of lymphocyte subsets are provided. Consequently, the $CD4^+$:$CD8^+$ ratio decreases with age in most (129,142,151,199), but not all (48,82) studies. A child's age is, therefore, an important consideration when interpreting the clinical utility of this ratio, as previously proposed (72). As a proportion of the total lymphocyte pool, natural killer (NK) cells are low during infancy and tend to increase with age in some (1, 12, 129, 199), but not all (48, 77, 82, 152, 199) studies. Some of the discrepancy regarding changes in NK cells with age is likely related to choice of surface antigen to represent the NK cell population. Not all studies used the $CD3^-CD16^+CD56^+$ phenotype, and it is unclear whether cells expressing high or low levels of CD16 or CD56 change during growth in a similar fashion. Despite a low proportion of NK cells during early life, a higher total lymphocyte count partially

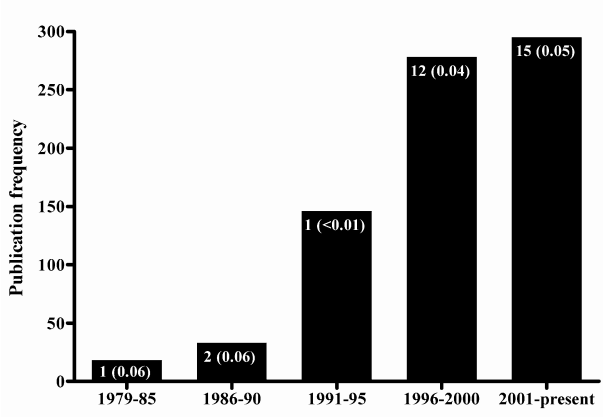


Figure 1: Publication frequency of paediatric exercise immunology studies in relation to an estimate of the total number of studies published in the field. Bars indicate frequency of total studies; inset numbers indicate paediatric studies (number in parenthesis reflects paediatric studies as a percentage of total studies). Data are derived from a PubMed search performed on September 30, 2005 (keywords: "exercise" AND "immune", limited to Human and English language studies), reference lists of relevant articles, and author's personal library.

offsets any absolute NK cell deficiency. A more consistent effect of age on immune development is a decrease in both the B cell proportion and count (48,77,78,82,142,151,152,199). In addition to significant age-related changes in concentrations, there are also functional changes that occur throughout childhood. Functional development of the immune system can be characterised by a gradual decrease in the proportion of $CD45RA^+$ cells and a reciprocal increase in the proportion of $CD45RO^+$ cells (48,82,129,152). This age-related increase in memory status results from antigenic experience and is associated with maturation of cytokine production. Cytokine production in response to *in vitro* stimulation, for example, progressively increases throughout childhood (46,90,158), but remains lower in children than in adults (25,46,62,90,96). This lower cytokine response to stimulation in children is associated with a lower proportion of $CD45RO^+$ memory lymphocytes (25,62). Several NK cell characteristics including cytotoxicity, recycling and target binding can achieve adult-like status by the first year of life (196). These may be additional mechanisms for a child to help compensate for a low proportion of NK cells, as indicated above. In contrast to the abundance of studies reporting age-related changes in cellular immunity, there has been little effort to describe changes in plasma levels of cytokines as a function of age. One study reported that interleukin-6 (IL-6) increased and tumour necrosis factor-$\alpha$ (TNF-$\alpha$) decreased from 3 to 17 years of age (147), whereas another study did not find an effect of age on IL-6, IL-8 or TNF-$\alpha$ levels from 1 to 18 years of age (97). A number of studies from Cooper and colleagues (110-113,149,150,182) have measured IL-6 and TNF-$\alpha$ in children using the same assay and show no substantial variation in resting concentrations according to chronological age.

**Changes with biological age**

While the effects of chronological age *per se* on the immune system are fairly well documented, many studies are weakened by the practice of compiling values from a wide range of ages into a single group average. A widely referenced publication on age-related changes in lymphocyte subsets (48), for example, classified one group of children by an age range of 7 to 17 years. This method, although not uncommon, effectively ignores the entire period of puberty and any potential influence of puberty-related events (e.g., alterations in sex hormone levels) on the outcome measures. This author is aware of only one publication that related immunological measures to a marker of biological age (11). In this study, Tanner stages (defining characteristic not reported) in boys, but not in girls, were positively correlated with B cell counts and the proportion of $CD3^+$ T cells. These relationships, however, may have been skewed because very few numbers of subjects were categorized as late or post-pubertal (i.e., Tanner 4 and 5). When the girls were divided based on pre- or post-menarcheal status, the total leukocyte and lymphocyte, $CD3^+$, $CD3^+CD4^+$, and NK cell counts and the proportion of NK cells were higher in the pre-menarcheal girls. A limitation in this study, however, was that children within various pubertal groups also varied in chronological age, and a stronger design would have assessed children of the same chronological age, but different biological ages. Clearly, more work is needed to describe development of the immune system as a function of puberty in boys and girls.

### Influence of sex

With few exceptions, there has been little evidence for differences in components of the immune system between boys and girls during childhood. In a large group of 8- to 12-year-old children, girls, as compared with boys, had higher proportions and absolute counts of total T cells and $CD4^+$ cells, but a lower proportion of NK cells (12). During adolescence, however, it has been reported that girls have higher total $CD4^+$ cell counts (12,145) and either higher (145) or lower (12) B cell counts. Adolescent girls also appear to have higher proportions of total T lymphocytes and $CD4^+$ cells and a lower proportion of B cells (12,183), a lower proportion of NK cells (12), and a higher NK cell count (145). Other changes in cell populations noted between sexes during the adolescence (183), likely serve as a transition into adult-like status.

### Summary

Progression through childhood and adolescence is associated with significant changes in various aspects of the immune system. Female sex also appears to play an important role in immune development beginning in the adolescent years, likely related to reproductive maturation. Collectively, these observations of the immune system under resting conditions provide compelling evidence that immune responses to physiological stress (i.e., exercise) may also change as a function of growth.

## Effects of acute exercise on the immune system

### Overview

Similar to the adult response, an acute bout of exercise in children and adolescents transiently affects numerous aspects of the immune system in an intensity- and duration-dependent manner. Although exercise-induced perturbations to cellular and soluble factors are generally short-lived, accumulated changes over time may alter overall immune status. In the following sections, commonly reported aspects of the immune system and their response to acute exercise are considered.

### sIgA

Studies of mucosal immune responses to exercise in children are extremely rare and have focused on a limited aspect of mucosal immunity, namely sIgA. Of the few available studies, young girls (52) have been shown to experience significant reductions in sIgA concentration following acute exercise, whereas older adolescent girls (120,126) and boys (120) have not. Post-exercise sIgA secretion rates, however, were significantly depressed relative to pre-exercise values in all of these studies. In a study of pre- and post-pubescent boys (171), sIgA levels were slightly but significantly elevated following basketball practice and game situations. Changes in total salivary protein, however, were not corrected for in this study, nor were secretion rates provided. An important determinant of the sIgA response to acute exercise in adults appears to be exercise intensity (63). This also seems to be the case for children insofar as sIgA levels were reported to be enhanced following moderate intensity exercise, but depressed following high intensity (43). Collectively, the above studies suggest that the pattern of sIgA responses to acute exercise in children is quite similar to that of adults. It is note-

worthy, however, that no direct comparisons between children and adults have been made to compare the magnitude of change (e.g., depression) in response to comparable exercise stress. Repeatedly depressed sIgA levels due to regular bouts of high-intensity acute exercise may have particular relevance for the young athlete's susceptibility to respiratory infections. Another unresolved issue is whether training status influences sIgA alterations in response to acute exercise in children and adolescents. To date, there have been no direct comparisons between trained and untrained youth in this regard, but it has been demonstrated (126) that young female tennis players with the greatest exercise-induced reduction in sIgA secretion rate, but not concentration, also had the highest incidence of upper respiratory tract infection (URTI). This latter study, however, included subjects up to the age of 21 years and therefore cannot be specifically considered a paediatric study.

**Neutrophils**

During exercise, neutrophils are mobilised into the peripheral circulation most likely from the bone marrow and other marginated pools (e.g., lungs) resulting in an elevated blood concentration. While several paediatric studies have determined the immediate neutrophil response to acute exercise (Table 1), few have followed changes in neutrophil cell counts into the immediate recovery period (19,20,155,179). This is an important consideration because a classical immune-related response to high-intensity exercise in the adult literature is a sustained neutrophilia during the one to five hours following exercise (132). Although one study (155) reported recovery of neutrophil cell counts to be faster in children vs. adults, interpretation of this finding was clouded by the fact that the exercise tasks were different in duration and intensity for the two age groups. We have found that while the neutrophil response *during* exercise is quite comparable among children, adolescents, and adults (179, 181), the post-exercise recovery of neutrophil cell counts is faster in children than in both adolescents (181) and adults (179).

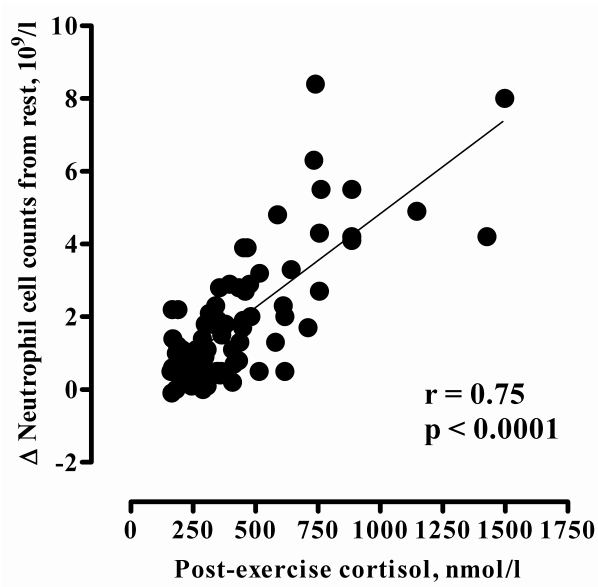


Figure 2. Relationship between recovery neutrophilia and post-exercise cortisol concentrations in children, adolescents, and adults. Data are from refs 179 and 181 and unpublished observations. Exercise task was 60 min cycling @ 70% $VO_{2max}$.

Table 1. Changes in neutrophil cell counts in response to acute exercise in children and adolescents.

| Ref | No. of subjects (sex) | Age | Mode | Duration | Intensity | Sampling Time | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Pre | Post | Recovery |
| | | | | ***Aerobic exercise*** | | | | |
| (179) | 12 (M) | 9-10 | Cycling | 60 min | 70% $VO_{2max}$ | 2.5 ± 0.3 | 3.5 ± 0.4[1] | 3.6 ± 0.5[4] |
| (181) | 14/20 (F/M) | 12 | Cycling | 60 min | 70% $VO_{2max}$ | 2.1 ± 0.2 | 3.4 ± 0.3[1] | 3.7 ± 0.4[4] |
| | 11/13 (F/M) | 14 | | | | 2.5 ± 0.3 | 4.1 ± 0.6 | 5.0 ± 0.7 |
| (192) | 7 gymnasts (F) | 10-12 | Treadmill | 20 min | 170-180 bpm | 2.7 ± 0.2 | 3.6 ± 0.3[1] | 3.1 ± 0.2[2] |
| | 6 controls (F) | | | | | 3.6 ± 0.4 | 4.7 ± 0.5 | 3.5 ± 0.3 |
| (155) | 9/2 (M/F) | 10.3 ± 0.6 | Cycling | 30 min | $V_{th}$ | 3.0 ± 0.2 | 3.8 ± 0.3[1] | 3.3 ± 0.3[3] |
| (134) | 6/3 (F/M) | 12.0 ± 0.6 | Cycling | 20 min | > $V_{th}$* | 4.2 ± 0.6 | 5.6 ± 0.8[1] | N/M |
| | 6/3 (F/M) | 10.0 ± 0.2 | Soccer practice | 90 min | N/P | 3.3 ± 0.7 | 4.5 ± 0.8[1] | N/M |
| (120) | 10/10 (F/M) tennis players | 14-18 | Tennis practice | 120 min | N/P | 3.4 ± 0.0 | 5.8 ± 0.1[1] | 5.1 ± 0.1[4] |
| (109) | 11 wrestlers (M) | 14-18.5 | Wrestling practice | 90 min | N/P | 3.9 ± 0.3 | 7.7 ± 0.9[1] | N/M |
| (112) | 10 water polo players (F) | 14-16 | Water polo practice | 90 min | N/P | 4.7 ± 0.5 | 9.6 ± 1.0[1] | N/M |
| (19) | 6/9 (M/F) | 8-18 | $VO_{2max}$ test | ~7.5 min | Increasing | 2.9 ± 0.2 | 3.6 ± 0.3[5] | 3.2 ± 0.3[4] |
| (26) | 9 track and field athletes | N/P | Stair-climbing | 10 min | N/P | 4.0 ± 0.5 | 5.0 ± 0.7[6] | N/M |
| | | | | ***Anaerobic exercise*** | | | | |
| (194) | 7 gymnasts (F) | 10-12 | Cycling | 30 sec | 7.5 Watts/kg | 3.0 ± 0.2 | 3.7 ± 0.2[1] | 3.5 ± 0.3[2] |
| | 6 controls (F) | | | | 5.7 Watts/kg | 3.5 ± 0.5 | 3.9 ± 0.3 | 3.3 ± 0.3 |
| (20) | 16 swimmers | 8-17 | Cycling | 30 sec | 7.8 Watts/kg | 2.6 ± 0.2 | 3.1 ± 0.2[5] | 2.7 ± 0.2[4] |
| | 17 non-swimmers | | | | 7.0 Watts/kg | 3.2 ± 0.2 | 3.7 ± 0.3 | 3.3 ± 0.2 |

Neutrophil cell counts are mean ± SEM given in $10^9$ cells/l. Ref, reference; bpm, beats per minute; $V_{th}$, ventilatory threshold; N/P, not provided; N/M, not measured; $VO_{2max}$, maximal oxygen uptake. *refers to an intensity equal to 50% of the difference between $VO_{2max}$ and $V_{th}$. Samples collected at [1]immediately after exercise, [2]24h after exercise, [3]30 min after exercise, [4]60 min after exercise, [5]3 min after exercise, [6]4-5 min after exercise.

On the one hand, elevated cortisol levels achieved by the preceding exercise may contribute to this recovery neutrophilia (103, 132). In our studies of children, adolescents, and adults, individuals with higher post-exercise cortisol levels also demonstrated higher recovery neutrophil cell counts (Figure 2). However, cortisol levels in all age groups, except adult men, actually decreased over time, despite the imposed bout of strenuous exercise (B.W. Timmons and O Bar-Or, unpublished observations). Moreover, elevated cortisol levels are not necessarily a prerequisite of recovery neutrophilia in adults (154). Another potential mediator of neutrophil mobilisation during and following exercise may be the cytokine IL-6, as previously demonstrated in adults (164). A direct statistical association between IL-6 and neutrophil cell counts during exercise in humans has been reported (170,178,197), and IL-6 infusion into rats (185) and rabbits (169) induces an immediate increase in systemic levels of neutrophils. Alternatively, recovery neutrophilia may reflect an inflammatory-related response to exercise-induced muscle damage (168,170), independent of any hormone effect. This possibility is consistent with the findings of previous paediatric studies, which demonstrated that markers of muscle damage following eccentrically-biased exercise are lower in children than in adults (4,100,160). Consequently, total muscle mass may be an important determinant of the degree of recovery neutrophilia. Indeed, we found that recovery neutrophilia was weakly, but significantly, correlated with fat-free mass in healthy children and adolescents (181). It may be, therefore, that older or more physically mature adolescents possess the capacity to recruit more muscle mass during exercise, thus contributing, in part, to a greater stimulus to the immune system.

A major limitation in the available paediatric literature is a lack of studies reporting the effects of acute exercise on neutrophil function *per se*. In fact, only one paediatric study (192) has reported the effects of acute exercise on neutrophil function; twenty min of treadmill running in pre-pubertal girls was found to differentially influence various aspects of *in vitro* neutrophil function. PMA-induced superoxide anion release, for example, was found to be reduced immediately after exercise whereas neutrophil chemotaxis, bactericidal activity and fMLP-induced superoxide anion release were not (192). Twenty-four hr later, PMA-induced superoxide anion release and neutrophil chemotaxis were now suppressed relative to pre-exercise values and the other measures were normal (192). It is also interesting to note that the gymnasts experienced a relatively larger reduction in chemotaxis (↓38%), as compared with the control girls (↓11%), but this difference was not statistically significant (192). Moreover, the decline in chemotaxis function in the control group was ~64% less than that reported by the same research group for untrained women performing similar exercise (193), whereas the decline in the gymnasts was quite comparable to that of the trained adults in this same study (193). It may be, therefore, that certain aspects of neutrophil function respond differently to exercise in children and adults depending on their training or fitness status, with smaller differences between trained or fitter individuals. There is no strong evidence, however, that the acute effects of exercise on neutrophil cell counts or function are different between trained and untrained children (20,155,192,194).

**NK cells**

One of the most studied aspects of the immune system in terms of exercise responses has been the NK cell population. The sensitivity of NK cells to physiological stress is striking, and given their direct involvement in anti-viral (15) and anti-cancer (22) defences and potent cytotoxicity (33), these cells could be a link between regular physical activity and overall health status. It is therefore not surprising that NK cells are also the most responsive cell type to exercise in studies of children and adolescents (19,20,45,109,112,120,134,155,179,181,194), as listed in Table 2. Although some evidence of a puberty-related effect on the NK cell response to short-term supra-maximal exercise was offered by Boas and colleagues (20), the first child-adult comparison (155) found that the children's response was ~40% less than that of the adults following the same amount of exercise time. However, due to the previously mentioned methodological limitations of this study and to the fact that different cell surface markers were used to enumerate NK cells in each group (CD16 *vs*. CD56) it remained unclear as to the extent of child-adult differences. A clear child-adult difference in the NK cell response to standardised, high-intensity exercise (60 min cycling @ 70% $VO_{2max}$) was later demonstrated (179). Interestingly, the magnitude of the NK cell response was also ~40% less in the boys, as compared with the men in this study (179). In follow-up studies, we have found the exercise-induced increase in NK cell counts to be quite comparable

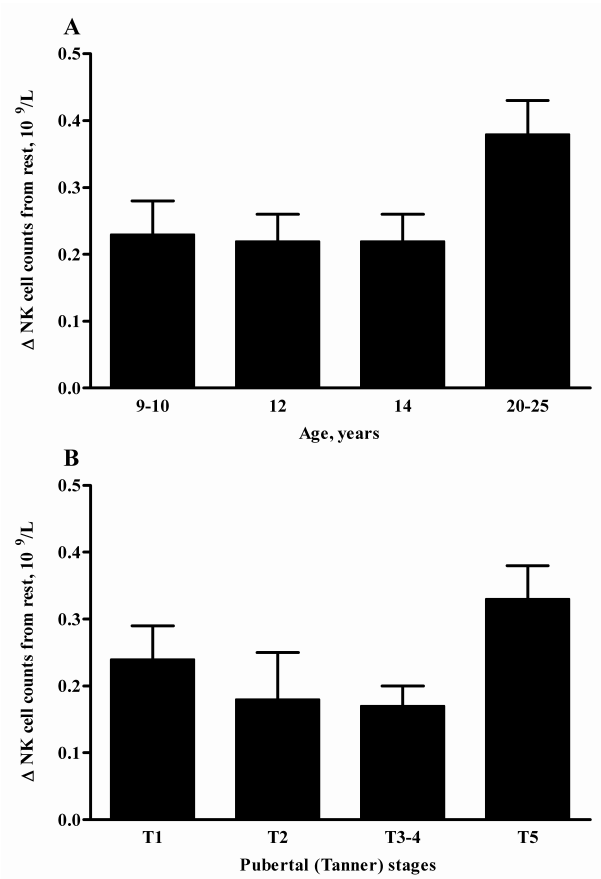


Figure 3. NK cell ($CD3^{-}CD16^{+}CD56^{+}$) response to exercise in male children, adolescents and adults according to chronological (A) and biological (B) age. Values are the change (Δ) in cell counts determined immediately at the end of exercise (60 min cycling @ 70% $VO_{2max}$) from pre-exercise values and are expressed as mean ± SEM. Data are redrawn from refs 179 and 181.

among male children and adolescents, but lower than in adult men (Figure 3A). In contrast, the magnitude of the NK cell response to strenuous exercise appears to be suppressed during puberty when the same subjects are categorised according to pubertal development (Figure 3B). It is also evident that female adolescents, but not younger girls, experience even greater NK cell responses to exercise (181). This age × sex interaction may be related to reproductive maturation since adult women also experience a larger exercise-induced lymphocytosis, as compared with men (40,177). However, acute estrogen supplementation (8 days) in healthy men does not enhance the lymphocyte response to endurance exercise (176).

Given the sensitivity of NK cells to catecholamine changes (84,85), the above observations might imply a lower exercise-induced catecholamine response in children, as compared with adults, and in males, as compared with females. Limited evidence suggests that catecholamine responses to exercise may be smaller in children vs. adults (144), but that the epinephrine response, for example, is generally lower in females vs. males (23,38,80). Moreover, we have not found significant correlations between exercise-induced changes in NK cell counts and either post-exercise epinephrine or norepinephrine levels among children and adolescents (B.W. Timmons and O Bar-Or, unpublished observations). In prepubescent, as compared with mature, rats a relative resistance to adrenergic suppression of NK cells has been demonstrated (130), suggesting an inherent deficiency in the cellular response to mediators of stress. Whether this invulnerability to stress becomes more pronounced *during* puberty is unknown, but it would be consistent with our findings in boys. In humans, β-adrenergic receptor density on lymphocytes increases with chronological age throughout childhood and adolescence (57,139), as does the isoprenaline-induced increase in intracellular levels of cyclic AMP (57), findings that might help explain the child-adult difference in NK cell sensitivity at the same relative intensity of exercise. This explanation, however, can not completely account for the lack of age effect *during* childhood. Sex-based differences in the sensitivity of NK cells to exercise may be related to a greater lymphocyte $\beta_2$-adrenergic receptor density (191) and post-receptor activity (71,104) in females, as compared with males. An overall greater influx of NK cells may be a compensatory mechanism to offset lower NK cell cytotoxicity in females (14,201).

Similar to the neutrophil story, there are few investigations into the effects of acute exercise on NK cell function in children and adolescents. Typically, studies reporting such effects have relied on the K562 assay as a measure of NK cell cytotoxicity. In response to a Wingate anaerobic test (WanT) (20) or $VO_{2max}$ test (19), NK cell cytotoxicity increased in young swimmers and non-swimmers. By 60 min of recovery from these activities, NK cell cytotoxicity was found to return to pre-exercise values in swimmers (20) and in healthy youth (19), but declined below pre-exercise values in non-swimmers (20). The discrepancy in these findings from the same research group can most likely be ascribed to differences in the nature of the exercise tasks. In response to 30 min of aerobic exercise, NK cell cytotoxicity did not change in children, despite an increase in NK cell counts (155). Interestingly, NK cell cytotoxicity did increase concomitantly with NK cell counts in adults (155). Thirty min following the end of exercise, NK cytotoxicity was reduced in the children (~25%), but to a greater degree in the adults (~50%); the adults cycled for 30 additional minutes, however (155).

Table 2. Changes in NK cell counts in response to acute exercise in children and adolescents.

| Ref | No. of subjects (sex) | Age | Mode | Duration | Intensity | Sampling Time | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Pre | Post | Recovery |
| | | | ***Aerobic exercise*** | | | | | |
| (179) | 12 (M) | 9-10 | Cycling | 60 min | 70% $VO_{2max}$ | 0.21 ± 0.03 | 0.44 ± 0.07[1] | 0.21 ± 0.03[4] |
| (181) | 14/20 (F/M) | 12 | Cycling | 60 min | 70% $VO_{2max}$ | 0.15 ± 0.02 | 0.35 ± 0.06[1] | 0.10 ± 0.02[4] |
| | 11/13 (F/M) | 14 | | | | 0.15 ± 0.02 | 0.43 ± 0.07 | 0.10 ± 0.02 |
| (45) | 7 gymnasts (F) | 10-12 | Treadmill | 20 min | 170-180 bpm | 0.16 ± 0.05 | 0.26 ± 0.05[1] | 0.23 ± 0.05[2] |
| | 6 controls (F) | | | | | 0.12 ± 0.02 | 0.27 ± 0.04 | 0.14 ± 0.02 |
| (155) | 9/2 (M/F) | 10.3 ± 0.6 | Cycling | 30 min | $V_{th}$ | 0.29 ± 0.03 | 0.47 ± 0.07[1] | 0.37 ± 0.07[3] |
| (134) | 6/3 (F/M) | 12.0 ± 0.6 | Cycling | 20 min | > $V_{th}$* | 0.32 ± 0.04 | 0.74 ± 0.09[1] | N/M |
| | 6/3 (F/M | 10.0 ± 0.2 | Soccer practice | 90 min | N/P | 0.37 ± 0.04 | 0.40 ± 0.07[1] | N/M |
| (120) | 10/10 (F/M) tennis players | 14-18 | Tennis practice | 120 min | N/P | 0.58 ± 0.01 | 0.47 ± 0.01[1] | 0.26 ± 0.01[4] |
| (109) | 11 wrestlers (M) | 14-18.5 | Wrestling practice | 90 min | N/P | 0.43 ± 0.05 | 1.47 ± 0.21[1] | N/M |
| (112) | 10 water polo players (F) | 14-16 | Water polo practice | 90 min | N/P | 0.31 ± 0.04 | 0.80 ± 0.11[1] | N/M |
| (19) | 6/9 (M/F) | 8-18 | $VO_{2max}$ test | ~7.5 min | Increasing | 0.19 ± 0.02 | 0.87 ± 0.08[5] | 0.19 ± 0.02[4] |
| | | | ***Anaerobic exercise*** | | | | | |
| (194) | 7 gymnasts (F) | 10-12 | Cycling | 30 sec | 7.5 Watts/kg | 0.16 ± 0.02 | 0.46 ± 0.12[1] | 0.23 ± 0.05[2] |
| | 6 controls (F) | | | | 5.7 Watts/kg | 0.09 ± 0.02 | 0.33 ± 0.11 | 0.17 ± 0.03 |
| (20) | 16 swimmers | | | | | | | |
| | 17 non-swimmers | 8-17 | Cycling | 30 sec | 7.8 Watts/kg | 0.24 ± 0.04 | 1.26 ± 0.15[5] | 0.25 ± 0.04[4] |
| | | | | | 7.0 Watts/kg | 0.43 ± 0.07 | 1.31 ± 0.15 | 0.27 ± 0.04 |

NK cell counts are mean ± SEM given in $10^9$ cells/l. Ref, reference; bpm, beats per minute; $V_{th}$, ventilatory threshold; N/P, not provided; N/M, not measured; $VO_{2max}$, maximal oxygen uptake. *refers to an intensity equal to 50% of the difference between $VO_{2max}$ and $V_{th}$. Samples collected at [1]immediately after exercise, [2]24h after exercise, [3]30 min after exercise, [4]60 min after exercise, [5]3 min after exercise, [6]4-5 min after exercise.

**T cells**

Unlike NK cells, the proportion of total T cells (i.e., $CD3^+$ cells) in the peripheral circulation generally declines during exercise. However, due to an overall exercise-induced lymphocytosis T cell counts increase, with the magnitude of increase greater for $CD8^+$ than for $CD4^+$ cells. This preferential mobilisation in cytotoxic T cells is also found in the paediatric literature and generally results in a reduced $CD4^+$:$CD8^+$ ratio during exercise (19, 20, 26, 45, 109, 112, 134, 155, 181, 194). Notwithstanding a lack of direct child-adult comparisons in the literature, there exists some evidence that this ratio is lowered during exercise to a greater degree in adults than in children and adolescents. Following a WanT, for example, two paediatric studies have reported reductions in the $CD4^+$:$CD8^+$ ratio of ~15% (194) and 17% (20), whereas Nieman and colleagues (119) noted a reduction of ~31% in adults. In general, an exercise-induced drop in the $CD4^+$:$CD8^+$ ratio rebounds by 60 min of recovery in children, adolescents and adults, but the child-adult differences *during* exercise are consistent with a smaller overall stress to the immune system in younger individuals.

An important distinction in the T cell response to exercise is the assessment of functional status of mobilised cells. Early work (56), for example, proposed that exercise recruited $CD8^+$ T cells with a "naive" phenotype (i.e., $CD45RO^-$), whereas a later investigation (59) found roughly equal recruitment of "memory" cells (i.e., $CD45RO^+$). It has also been demonstrated that of the $CD8^+$ cells mobilised, the majority of these do not express the L-selectin adhesion molecule CD62L (59,60,67,91), which typically reflects memory cells. Given the transition from naïve to memory T cells during growth (e.g., 48,82,129,152), one might expect young children to preferentially mobilise naïve cells. Based on studies by Cooper and colleagues conducted with young children and older adolescents, this is not necessarily the case. In adolescent boys (109) and girls (112), $CD8^+CD62L^-$ cells were preferentially mobilised in response to field-type activity. In young children (mean age of 12 years), $CD8^+CD62L^-$ cells were also selectively mobilised, but the difference between subset responses was less than that in the adolescents. Interestingly, in the youngest children studied (mean age of 10 years), the $CD8^+CD62L^+$ cell population increased slightly more than the CD8+$CD62L^-$ population (134). Notwithstanding the difficulty in comparing field studies that do not control for exercise intensity and duration, these findings from the same laboratory suggest that young children may, in fact, selectively mobilise naïve T cells in response to exercise, as this cell population would represent the largest available compartment of T cells. We have assessed the effect of strenuous exercise on the expression of CD45RO on $CD8^+$ T cells in 12- and 14-yr-old youth and found that $CD45RO^+$ cells are preferentially mobilised in both groups (B.W. Timmons and O. Bar-Or, unpublished observations). However, we did not measure CD62L status and did not include a younger age group in whom T cell changes may be more equally distributed between naïve and memory cells. There is also some evidence that exercise increases T cell activation status, although there were no changes in the activation marker, CD69 (55). Likewise, other adult studies have not found exercise-induced increases in the percentage of T cells expressing CD69 (68,143). Children and adolescents do, however, experience a small but significant increase in the proportion of T cells expressing $CD69^+$ (Figure 4), without an increase in the relative density of CD69 (i.e., median fluo-

rescence intensity) on the cell surface (B.W. Timmons and O. Bar-Or, unpublished observations). This latter finding suggests that exercise may not increase activation status *per se*, but rather mobilises cells already expressing CD69. Another example of child-adult differences in T cell responses exists during the recovery period from high intensity exercise. While adults typically experience an overall lymphopenia, characterised by a suppression of T cell counts (132), young children do not (179), indicating a much faster recovery of T cells. It remains to be determined, however, whether this quick recovery of T cell status in children results in maintained functional status (e.g., lymphocyte proliferation) during the recovery period.

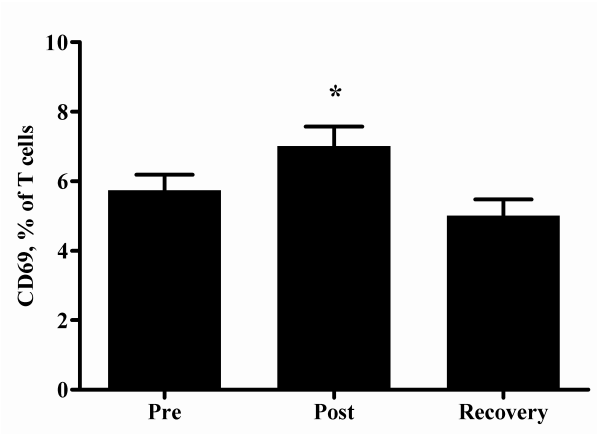


Figure 4: Percentage of T cells ($CD3^+$) expressing CD69 before, immediately after, and 60 min after the end of exercise in children and adolescents. Values are mean ± SEM (unpublished observations). *significantly different from Pre ($p = 0.002$) based on one-way ANOVA, with Tukey's post-hoc test.

## IL-6

Of considerable interest in recent years has been the observation that contracting skeletal muscle can produce and release IL-6 (165). The role of this cytokine in metabolic adjustments to exercise has since been extensively studied (49), and the release of IL-6 from muscle during contraction has been argued (135) to reflect the anti-inflammatory properties of exercise. For obvious ethical reasons, it is impossible to study muscle release of IL-6 during exercise in children. However, if one assumes that the magnitude of the exercise-induced increase in IL-6 can be accounted for by muscle production and release (165), some interesting observations can be made. Under conditions of standardised exercise duration and intensity, the magnitude of the IL-6 response increases as a function of chronological and biological age (Figure 5). Most paediatric studies (110,112,120,133,149) have investigated the impact of exercise on circulating IL-6 levels under field conditions, which do not allow for adequate experimental control to make comparisons among different groups (e.g., children vs. adults). However, other studies investigating the IL-6 response to cycling exercise at a defined work-rate (182) are consistent with the observations in Figure 5, by showing that children's responses are ~50% lower than what has been reported for adults under similar exercise conditions (172).

That the magnitude of the IL-6 response to exercise is associated with advancing chronological age and physical maturity suggests that this cytokine may be important in global processes of growth. The lower IL-6 response during

and following exercise is consistent with a lower inflammatory response in younger children. Indeed, transgenic mice expressing high levels of circulating IL-6 have reduced growth rates, which are partially reversed with administration of antibody to the IL-6 receptor (39). In children and adolescents with systemic juvenile rheumatoid arthritis, a condition characterised by stunted growth, insulin-like growth factor-1 (IGF-1) levels are lower than normal and correlate negatively with IL-6 levels (39). On the other hand, IL-6 induces expression of vascular endothelial growth factor (29), a potent angiogenic factor, which is likely to be important in muscle adaptation to exercise. Given the constitutive expression of IL-6 in skeletal muscle (162) and its release during contraction (165), it is tempting to suggest that comparatively smaller exercise-induced increases in IL-6 in children may be sufficient to serve an adaptive function, without compromising other anabolic mediators (e.g., IGF-1).

With respect to the metabolic roles of IL-6, the smaller increases in children may reflect differences in fuel selection during exercise. In this regard, IL-6 is thought to be released from muscle during exercise as a potential regulatory hormone to increase liver gluconeogenesis; for example, when muscle glycogen content is low (163). We (175) and others (99,102) have clearly demonstrated that children preferentially oxidise fat rather than carbohydrate as a source of endogenous fuel during exercise, and the rate of

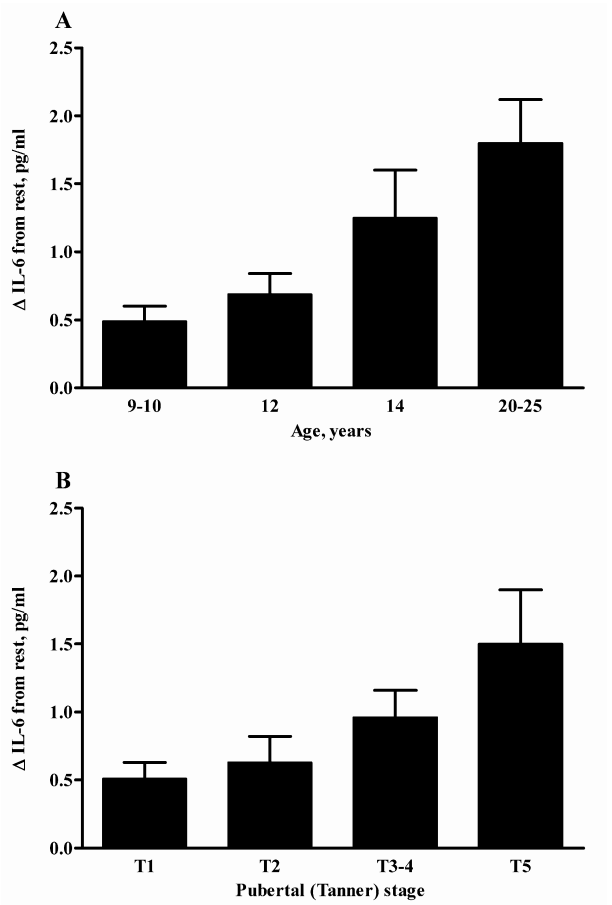


Figure 5: IL-6 response to exercise in male children, adolescents, and adults according to chronological (A) and biological (B) age. Values are the change (Δ) in cell counts determined immediately following exercise (60 min cycling @ 70% $VO_2$max) from pre-exercise values and are expressed as mean ± SEM. Data are redrawn from ref 181 and unpublished observations.

muscle glycogenolysis has also been shown to increase with age during childhood (47). Thus, if children's muscle glycogen levels are not lowered during exercise, because of a reliance on extra-muscular fuel sources (e.g., free fatty acids), the intracellular signalling for IL-6 release may also be reduced.

**TNF-α**

TNF-α is a pro-inflammatory cytokine and is important in the initiation of the inflammatory response to infection (13). Human muscle protein synthesis is inhibited by TNF-α (94), which may contribute to muscle atrophy associated with ageing (69). TNF-α is also produced and secreted by adipocytes (81,88) and is associated with insulin resistance (105). In children and adolescents, the magnitude of exercise-induced changes in TNF-α concentration is generally quite low (110,149,179,182) and may even be negative (112). From our studies of children, adolescents and adults, a varied pattern of response can be observed with low or negative net changes (relative to pre-exercise values) in the young individuals, as compared with a relatively larger response in the adults (Figure 6). Given the potentially negative consequences of elevated TNF-α levels, one reason for very low or no stress-induced increase in TNF-α in children may serve a protective function for tissue growth (e.g., muscle, bone, etc.). Recently, it was demonstrated that IL-6 may function as an antagonist to TNF-α (161). Therefore, the ratio of IL-6 to TNF-α may be a useful marker of the inflammatory environment during and following exercise. In this context, a high ratio would be interpreted as beneficial whereas a low ratio would be less appealing. Figure 7 highlights this "anti-inflammatory ratio" in children, adolescents and adults. These findings demonstrate that the anti-inflammatory ratio gradually decreases with age, with the exception of the highest ratio, which occurs in 14-yr-old children. Therefore, these cytokine data may be considered further support that children are relatively resistant to major inflammatory stress during and following exercise. Given the antagonism between inflammation and growth (39), this "inflammatory protection" would reflect an overall positive growth response by facilitating the anabolic effects of exercise.

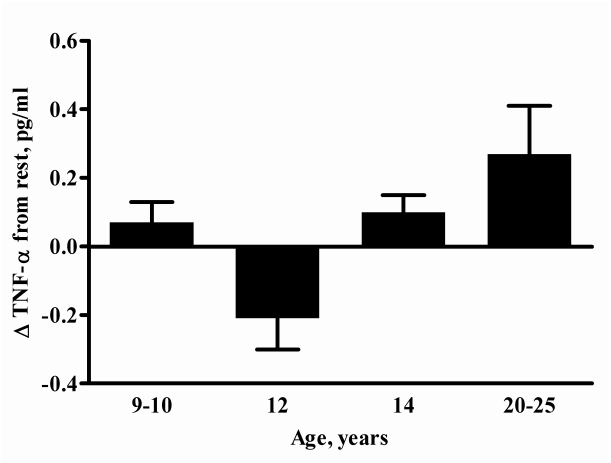


Figure 6: TNF-α response to exercise in male children, adolescents, and adults according to chronological age. Values are the change (Δ) in cell counts determined immediately following exercise (60 min cycling @ 70% $VO_{2max}$) from pre-exercise values and are expressed as mean ± SEM. Data are redrawn from ref 181 and unpublished observations.

**IL-8**

IL-8 plays a key role in early inflammatory events as a chemoattractant for neutrophils. Production of IL-8 at the site of inflammation is induced by pro-inflammatory cytokines like IL-1 and TNF-a. Plasma levels of IL-8 are also positively associated with fat mass in obese, but not lean, adults (167), suggesting a potential role in the low-grade inflammation associated with obesity (37). On the other hand, IL-8 is expressed in skeletal muscle and its expression can be increased with contraction (2,24), suggesting a possible role for IL-8 in muscle adaptation and growth. We have recently reported that plasma levels of IL-8 increase during recovery from strenuous exercise in children and adolescents (173). This novel finding may have a number of possible consequences, including recruitment of progenitor cells (i.e., $CD34^+$ cells) from the bone marrow during exercise (51). These progenitor cells could then differentiate into endothelial cells thus contributing to neovascularisation or, alternatively, actually incorporate into muscle tissue, as has been demonstrated in animal models (131). Another consequence of local production of IL-8 might relate to this cytokine's potent chemoattractant properties; IL-8 could induce the recruitment of neutrophils and other immune cells into skeletal muscle. Preliminary work shows that immune cells mobilised during exercise can express GH and IGF-1 (202). It is therefore conceivable that release of these factors within muscle may then contribute to muscle regeneration/adaptation and growth. Clarifying the role of exercise-induced cytokine changes, and IL-8 in particular, in normal tissue growth and development in children should be an exciting area of future work.

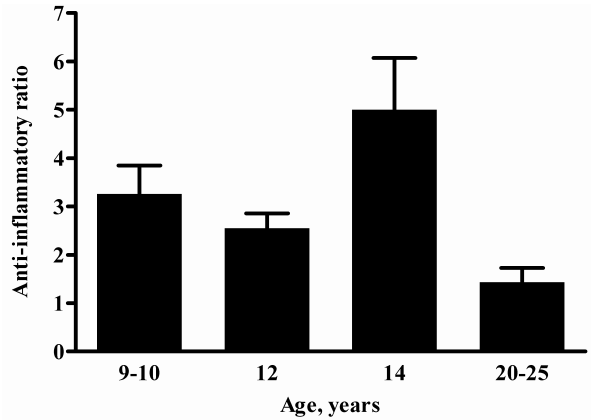


Figure 7. Anti-inflammatory ratio immediately following exercise in male children, adolescents, and adults according to chronological age. Values reflect the ratio of IL-6:TNF-α and are expressed as mean ± SEM. Calculations are based on data published in ref 181 and unpublished observations.

**Carbohydrate intake and immune changes in response to exercise in children**

That high-intensity, prolonged exercise leads to significant suppression of the number and function of various immune cells during recovery initiated a search for strategies to improve immune status under these conditions (122). Of the many investigated options, considerable research attention has focused on carbohydrate (CHO) supplementation, which when provided in the form of a sports drink during exercise, attenuates the rise in cell number and function and tends to speed the recovery of cells following exercise (115). The increase in plasma lev-

els of several cytokines is also attenuated with CHO intake (16,108,121,162), as is their expression in skeletal muscle with exercise (50,117).

Studies investigating the effects of CHO supplementation on the immune system in children and adolescents have been few. One study (120) reported immune changes in elite adolescent tennis players who drank a sports drink during practice. Although neutrophil cell counts increased significantly, lymphocyte and NK cell counts actually decreased with exercise and remained below pre-exercise levels 60 min into recovery (120). However, since there was no comparable trial with only water consumption (i.e., placebo), it was impossible to separate CHO and exercise effects in this study. Our group has demonstrated that CHO intake, as compared with flavoured water, significantly attenuates the exercise-induced rise in neutrophil and NK cell counts in children (179). Moreover, the innate immune system seems to be more sensitive to CHO intake in children than in adults. The attenuation of NK cells and neutrophils, for example, was observed following 60 min of exercise in boys, but not in men (179). In 12-yr-old boys (174) and girls (180), CHO can blunt the NK cell response after only 30 min of exercise. Although it has been suggested that high-intensity exercise lasting longer than two hours is required before significant effects of CHO intake on immunity are observed (116), this is clearly not the case in children. Likewise, recovery neutrophilia is completely abolished with CHO intake in children, but is only partially blunted in adults (179). In essence, the extra energy provided during exercise seems to minimise the disruption to immune homeostasis. However, the acute effects of CHO intake on perturbations to NK cells and other markers of immunity have not yet been linked to a long-term reduction in the incidence of URTI in either children or adults.

**Summary**

The above sections considered some of the effects of acute exercise on the immune system in children and adolescents. While the general pattern of immune responses is similar between children and adults, there are clear differences in the magnitude and direction of some changes, including those in NK cells, T cells, IL-6 and TNF-$\alpha$. Moreover, the child's immune system seems to be particularly sensitive to CHO intake during exercise, and female sex enhances the NK cell response, in particular. Although it is difficult to establish the exact mechanisms of action, the evidence would suggest that interactions between immune cells and hormones and the initiation of cytokine production during acute exercise may be regulated differently in children than in adults.

## Effects of chronic exercise on the immune system

**Overview**

Although there are few paediatric-specific data regarding training and immune function, some comparisons of resting immune status between athletic and non-athletic youth have been made. In contrast, several adult studies have compared resting immune function between trained and untrained individuals. Based on the latter comparisons, the general consensus is that the immune system of a trained individual is more similar than dissimilar to that of an untrained individual (98,114,153).

**sIgA**

In adult athletes, depressed sIgA levels have been associated with an increased risk of URTI during a training season (65). Among young athletes, resting sIgA levels do not seem to be affected by periods of training in young gymnasts (52) or tennis players (126), nor are they related to chronic PA in young children (28). It may be that the training practices of young athletes are not sufficiently intense to produce clinically relevant reductions in sIgA. It may also be possible that, similar to other aspects of the immune system, children are simply resistant to major perturbations induced by similar levels of exercise.

**Neutrophils**

Among adult athletes, some aspects of neutrophil function tend to be reduced, as compared with non-athletes, despite normal neutrophil cell counts (98,114). Smith et al. (159) proposed that this down-regulation of neutrophil status may be protective against perpetual chronic inflammation as a result of exercise-induced muscle damage. The evidence of a training effect on neutrophil function in children and adolescents is mixed. While resting neutrophil cell counts tend to be lower in the trained *vs*. untrained state (20,148,155,192), only one study (20) found this difference to be statistically significant. Unfortunately, meaningful insight into whether neutrophil function *per se* is depressed in the young athlete is lacking due to an insufficient number of studies. Depending on the particular aspect of functional activity assessed, higher (148), lower (192), or the same (148,192) values can be found in trained youth, as compared with their non-athletic peers. The only study to compare neutrophil cell counts in healthy children before and after an exercise training program found no effect (155).

**NK cells**

In contrast to neutrophil function, some evidence suggests that NK cell cytotoxicity is higher in adult athletes, as compared with non-athletes (98,114). Similar training-related differences in NK cell function, however, have not been identified among young swimmers and non-swimmers (20). Likewise, NK cell counts are not statistically different in trained and untrained children (20,45), although values can be up to 80% lower in the trained state (20). Short-term (12 weeks) of exercise training in healthy children does not significantly influence NK cell counts or cytotoxicity at rest, although post-training cytotoxicity values were non-significantly reduced by 43%, as compared with pre-training levels (155). It was found, however, that training reduced stimulated NK cell cytotoxicity during recovery from acute exercise (155). Given the extreme lack of data, it is difficult to draw firm conclusions as to whether training status truly affects NK cell counts or function in youth.

**Cytokines**

To this author's knowledge, only two studies have investigated the effects of an exercise training intervention on cytokine levels in healthy children and adolescents. Scheett et al. (150) investigated the effects of a 5-wk endurance training program on various cytokines in pre- and early-pubertal boys, and, importantly, they included a control group. Plasma levels of IL-1β and TNF-α, but not IL-6 or IL-1ra were found to be increased following the training program, whereas all

cytokine levels slightly decreased in the control group (150). There were, however, pre-intervention differences in IL-6 and TNF-α between the groups. Whether initial cytokine levels mediate the response to training is unclear and was not addressed in this study. Another study from the same research team followed a group of adolescent wrestlers over a wrestling season (111). Following six weeks of training, IL-1ra and IL-6 were found to be elevated at rest, but declined thereafter during the remainder of the training and competition season (111). However, only the elevation in IL-1ra was statistically significant and other cytokines measured (TNF-α and IL-1β) did not change over time. Unfortunately, no control group was included to distinguish true effects of wrestling from changes due to time, and given the mixed cytokine responses, the significance of the results are not readily apparent.

**Summary**

Based on the available paediatric data, the resting immune status of the young athlete appears to be no different than that of their untrained peer. With respect to the cellular immune system, a prospective intervention of enhanced PA imparts little impact on immune function. Training-related changes in pro- and anti-inflammatory cytokines may be important to processes of tissue adaptation, as previously discussed, but more work is required to help clarify the contradictory results thus far. In a way, these findings might not be surprising considering the smaller perturbations to the immune system in response to acute bouts of activity. However, the "trainability" of children has long been an issue of contention among paediatric exercise scientists (144), and the findings with respect to the immune system seem no different.

## Physical activity and risk of infection

Based on the adult literature, most exercise immunology researchers (including this author) subscribe to the hypothesis that a moderate amount and intensity of physical activity (PA) enhances immune health (i.e., decreases risk of infection) whereas high volumes of high intensity exercise reduce immune function and, therefore, increases the risk of infection. Whether this hypothesis, coined the "J-curve" (74), holds true during childhood is unclear, and only a few studies have investigated the relationship between risk of infection and PA in youth.

Over a 12-month period, the incidence of respiratory infections was found not to be different between children who did or did not participate in sports (128). In most cases, however, a direct (as opposed to a J-curve) relationship between the incidence of URTI and PA among children and adolescents has been demonstrated (28,83,89). In other words, youth who are more active also experience fewer sickness days. Another important observation is that physically inactive children were ~3 times more likely to experience a recurrent acute respiratory infection (RARI), as compared with more active children, over a 2-year period (83). Moreover, the protective effect of PA against a RARI was also observed in children with allergies or who were overweight (83). In contrast to the evidence for a direct association between risk of infection and PA, participation in more than 5 sports activities per week increased the occurrence of common cold, cough/sputum, and fever symptoms in 10- to 17-yr-old boys and girls, whereas

participation in 3 to 4 sporting activities per week lowered the occurrence (187). Similarly, the association between a URTI symptom index and total daily energy expenditure was found to follow a J-curve relationship in elite female tennis players, with a higher index in the players expending the most energy (125). Although limited evidence suggests a protective effect of regular PA against respiratory infections in non-athletic children, the consequences of specific exercise training may be more detrimental to the young athlete's ability to combat infection. However, this apparent paradox between athletes and non-athletes may just as easily be explained by stresses associated with competition or differences in other factors such as sleep, nutrition, and other life stresses (e.g., time for school-work) rather than a different effect of exercise *per se*.

## Infection and illness in the young athlete

Team physicians, athletic therapists, and coaches might be called upon to provide advice on whether children and adolescents who are ill should maintain their PA routines or what strategies can be implemented to maintain optimal immune health in the face of repeated physiological stress. At present, health care professionals are forced to rely on common sense and some sparse guidelines based solely on the adult literature (124) to help navigate the above issues. In general, an athlete's exercise performance is reduced during acute illness (54), and there is also some evidence for this in the paediatric age range (140). More importantly, overall health of the young athlete may be compromised if intense exercise training continues during an infectious episode. It was noted early on that following intense exercise and competitive sport in boys, respiratory infections tended to progress toward pneumonia (34). Intense PA at the onset of paralytic poliomyelitis in children has been associated with greater severity of disease in a number of studies (73,79,146). Acute infectious episodes may also cause increased protein degradation and a temporary negative nitrogen balance (54). These consequences combined with the energy demands of exercise training have obvious implications for rapidly growing children. In these cases, children who continue to train during advanced stages of infection may demonstrate a temporary loss of lean muscle tissue. Such scenarios can be easily avoided by complete rest until symptoms resolve. The practice of exercising and training with an elevated core body temperature, due to fever may place added stress on a child's ability to efficiently thermoregulate during exercise, particularly in the heat. It is well-documented that children thermoregulate less efficiently during exercise under conditions of high heat stress, as compared with adults (9). Moreover, for a given level of dehydration, children tend to have a greater rise in core body temperature, as compared with adults (8). Collectively, these observations suggest that a young athlete who decides to exercise in the heat under febrile conditions could very well increase their risk of heat illness and that this should be avoided.

Among the general guidelines prepared for adult athletes, most authorities agree upon a "head-and-neck" rule whereby symptoms restricted to above the neck (e.g., common cold, runny nose, etc.) should not pose major threats to the individual and that exercise training may continue, albeit at a reduced rate (98,114,141). Signs and symptoms of systemic involvement (e.g., fever, body aches, etc.) should be taken more seriously with all PA discontinued. The amount

of recovery time necessary before resuming a normal training schedule depends on the severity of the preceding symptoms and any other complications, but most recommendations range from 2 weeks (74) to a month (141). At present, there are no data that would specifically contraindicate the application of these guidelines to the young athlete. If anything, adult guidelines may be over-generous given the overall smaller exercise-induced perturbation to many aspects of the immune system and faster recovery of immune status following exercise in children. It is essential, however, that the team physician or family doctor be consulted and provide consent before the young athlete resumes training and competition.

## Exercise and the immune system in paediatric clinical conditions

### Overview

Until now, this review has focused on the interaction between acute and chronic exercise and the immune system of healthy children and adolescents. The impact of exercise and PA on the immune system is also of interest in the paediatric clinic, because a number of paediatric conditions express a strong immune component. To this end, the following sections will briefly address some of the available immunology of exercise literature pertaining to childhood obesity, cystic fibrosis (CF), exercise-induced asthma (EIA), and acute lymphoblastic leukemia (ALL). These particular conditions have been chosen as they reflect this author's interests, but there are other important paediatric populations in which exercise may be of benefit in terms of immune function (e.g., juvenile rheumatoid arthritis).

### Childhood obesity

Although the state of overweight or obesity among children and adolescents is ultimately an issue of energy imbalance, there is some evidence of immune dysfunction in this population (118), although results have been mixed. On the other hand, many studies have documented an underlying state of low-grade inflammation. Initially, C-reactive protein (CRP) concentrations were found to increase linearly with adiposity in boys and girls (31). Subsequent studies have confirmed higher CRP levels in overweight or obese children *vs*. healthy-weight youth (53,93,138,186,189). In addition, the inflammatory-related cytokines TNF-α (5,66,70,106,138) and IL-6 (5,6,66,70,188) and total leukocyte count (186) are also elevated in overweight children. Collectively, this state of low-grade inflammation may contribute to insulin resistance and endothelial dysfunction, conditions that are increasing in prevalence among overweight youth. It is also unclear whether chronic exposure to inflammation has consequences for tissue growth. While overweight and obese children and adolescents appear to exhibit similar levels of muscle strength, as compared with their healthy-weight peers (17), it is noteworthy that the former group can present with reduced bone strength (44). It is therefore encouraging that enhanced PA can lower plasma levels of IL-6 in overweight and obese youth (6,58,87) presumably accompanied by lower TNF-α levels (although this cytokine was not measured in these studies). Moreover, physical fitness, even in overweight children, is associated with a more favourable cytokine profile (70). It remains unresolved, however, whether immune activation in overweight and obese youth is a consequence or a cause of the obese phenotype and its

associated complications. Surprisingly, there is only one report (to this author's knowledge) of immune changes in response to an acute bout of exercise in overweight or obese children. Although no indication of exercise duration or intensity was given, it was reported (32) that neutrophil cell counts increased by ~33% in 16 obese children in response to a cycling task. This magnitude of increase was very similar to the response of healthy-weight children (32).

**CF**

Given the increased life expectancy of children and adolescents with CF, a growing interest in their quality of life and overall well-being has emerged, with an important therapeutic role for enhanced PA (7). Although CF is characterised by an overactive immune system, few studies have investigated immune-related responses to acute exercise in these patients, and there appears to be a complete lack of studies describing the effects of long-term training studies on immune function. In comparison with age-, weight-, and height-matched peers, CF patients were found to have very similar responses of leukocyte and lymphocyte subsets and NK cells to a $VO_{2max}$ test (19). However, the subjects with CF in this study actually exercised for a full minute (or 17%) less than their healthy peers. Therefore, one might argue, given the comparable overall immune response to less exercise stress, that the CF patients did in fact exhibit an abnormal immune response. In line with this possibility is that the same research group found that the degree of change in lymphocyte and NK cell counts in response to a similar $VO_{2max}$ test was negatively correlated with the patient's $FEV_1$ as a percent of predicted for height, weight, and age (18). Thus, patients with more severe disease demonstrated a more pronounced immune response to exercise, consistent with an "overactive" immune system.

Another concern for children and adolescents with CF is the degree of underlying inflammation, which is particularly important as this may promote tissue catabolism. In young CF patients, a negative correlation between TNF-$\alpha$ and IGF-1 has been reported along with elevated serum IL-6 levels in this group, as compared with healthy children and adolescents (182). Consistent with the results of blood cell counts, the magnitude of the TNF-$\alpha$ and IL-6 response to standardised exercise was considerably higher in the CF patients, as compared with healthy controls (182). Interestingly, among those CF patients receiving ibuprofen therapy the cytokine response to exercise was blunted, but remained greater than healthy controls (182).

Collectively, the above studies suggest that children and adolescents with CF may experience over-activation of the immune system in response to brief, but intense, bouts of exercise. It will be important to identify whether regular exercise training and enhanced habitual PA can lower the inflammatory state observed in these patients. Such an effect may contribute to the numerous health benefits of enhanced PA previously reported in this population.

**EIA**

The vast majority of youth with EIA are able to engage in a physically active lifestyle, which includes competitive athletics. Among these individuals, mediators of inflammation are thought to be important in the pathogenesis of airway obstruction. Increases in neutrophil chemotactic activity, for example, accompany reduc-

tions in $FEV_1$ in children with EIA (95). A reduction in RANTES and an elevation in IL-8 have also been demonstrated (95). A strong correlation can also be found between the serum level of RANTES and peripheral blood eosinophil cell counts in children with a positive EIA test (21), and activation of eosinophils may be an important determinant of bronchial hyperresponsiveness in EIA (198). Indeed, eosinophils are believed to be of particular importance in determining the severity of EIA (3), as there are more eosinophils in the sputum of individuals with EIA vs. those without EIA (200). Considerable evidence also indicates that medication directed toward attenuating airway inflammation (e.g., steroids, leukotriene antagonists, etc.) can lessen the severity of EIA (3,127). While the health benefits of exercise training (e.g., improved fitness) for children with EIA have been recognised (190), there remains some controversy as to whether the severity of the condition can be ameliorated. In this regard, it will be interesting to determine whether exercise training lowers the degree of airway inflammation in children with EIA, thereby improving symptoms. One obvious consequence of such an effect might be a reduction in the amount of medication required by the child.

**ALL**

Theoretically, exercise of moderate intensity may help "boost" the immune system of cancer patients and might even improve efficiency of drug–cell interactions, given the cellular mobilisation in response to acute exercise. This author has received a number of testimonials describing a successful clinical outcome in children and adolescents who maintained regular PA during their cancer treatment. Empirical data to support the benefits of exercise on clinical outcomes are, however, nonexistent. Two groups (92,156) have investigated the effects of exercise on the immune system of children with ALL. In both studies, patients were tested during their maintenance chemotherapy (i.e., following induction of remission), and the pattern, magnitude, and direction of exercise-induced leukocytosis were comparable between children with ALL and otherwise healthy children. To further evaluate the interaction between exercise and the immune system in ALL patients, Shore and Shephard (156) recruited three patients to participate in an exercise training program for 12 weeks. When compared with pre-training levels, many of the immune parameters measured post-training were actually reduced, but in no instance did the differences reach statistical significance, likely due to the small number of subjects and thus low statistical power. Notwithstanding this problem, one encouraging finding was that NK cell cytotoxicity was non-significantly enhanced by ~132%. This is an encouraging finding because NK cell cytotoxicity reflects the capacity to kill cancerous cells, and studies with more patients are required to confirm or reject this finding. It is clear, however, that survivors of ALL should be monitored on an individual basis when recommencing regimens of PA. It is also clear that much more work is required in this area.

**Summary**

A number of paediatric conditions express a strong immune component, which may be affected by acute and chronic exercise. In most of the above examples, over-activation of the immune system is the culprit. Given the proposed anti-inflammatory effect of exercise (135), these conditions may therefore benefit from programs of enhanced PA through an immune-related mechanism.

## Summary and future considerations

This review has addressed exercise immunology literature that pertains to healthy children and adolescents and some of the literature regarding specific clinical paediatric conditions. In summary, children tend to be resistant to major exercise-induced perturbations to the immune system. This is characterised by smaller changes in NK cells, IL-6 and TNF-α in response to exercise. Consistent with the notion that children experience a faster physiological recovery from strenuous exercise than do adults (e.g., 10,75,76), the immune system of a child also tends to recover more quickly than that of an adult. The growing child may also possess inherent mechanisms to ensure an anti-inflammatory environment in response to physiological stress; a response that may be conducive to the anabolic effects of exercise. Literature pertaining to the relationship between risk of infection and PA is sparse, but for the general population of healthy active children, increased levels of PA are associated with reduced susceptibility to respiratory infections. In contrast, the available evidence would suggest that high volume sport training might increase the susceptibility to illness and infection. For the most part, guidelines derived from the adult literature should be appropriate for the young athlete, but more research would be welcome in this area given the increased sports participation among many youth today. Finally, exercise immunology has an important role in the paediatric clinic. Dysregulation of the immune system and its response to exercise in some paediatric conditions may provide valuable insights into mechanisms mediating the normal immune response to exercise.

In the future, research needs to clarify the orchestration between exercise, the immune system, and growth-related processes, including the influence of puberty on immune effects of acute and chronic exercise. The biological significance of this interaction is particularly germane for children with, or recovering from, an immune-related disease. A clearer understanding of the relationship between PA level and resistance to infection among children and adolescents is also of great interest. As with so many aspects of athletics, the young competitor is forced to rely on adult guidelines, and additional research in this area would serve as a considerable contribution to the management of young athletes. Another promising area for future research in paediatric exercise immunology will be to understand the relationship between physical activity and immune development in early childhood (e.g., < 5 years of age). Given the emerging problems of physical inactivity and overweight in youth and the possible links between immune dysfunction and prevalence of adult-like health disorders during childhood, an improved understanding of the relationship between physical activity and immune health during the growing years is essential.

## Acknowledgements

The author is supported by a Canadian Institutes of Health Research Industry-partnered (Gatorade Sports Science Institute) Post-Doctoral Fellowship. Financial support of the author's studies was provided by the Gatorade Sports Science Institute and BD Biosciences.

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