Effect of high-intensity training and Asthma on the $\dot{V}O_2$ kinetics of adolescents

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Short title: Effect of HIIT on $\dot{V}O_2$ kinetics in youth

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Abstract

Purpose: High-intensity interval training (HIIT) represents a potent stimulus to the dynamic oxygen uptake ($\dot{V}O_2$) response in adults but whether the same is evident in youth is unknown. HIIT has also been suggested to place a lower demand on the respiratory system, decreasing the likelihood of exacerbation in those with respiratory conditions, such as asthma.

Methods: Sixty-nine adolescents (13.6±0.9 years; 36 asthma) took part, 35 of which (17 asthma) participated in a 30-minute HIIT intervention three-times/week for six months. Each participant completed an incremental ramp test to volitional exhaustion and three heavy-intensity constant work-rate tests to determine the dynamic oxygen uptake ($\dot{V}O_2$), heart rate (HR) and deoxyhaemoglobin ([HHb]) response at baseline, mid-intervention, post-intervention and at a three-month follow-up.

Results: There was no influence of asthma at baseline or in response to the intervention. Participants in the intervention group demonstrated a faster $\dot{V}O_2$ time constant (τ_p) post-intervention (intervention: 29.2±5.7 vs. control: 34.2±6.5 s; P=0.003), with these differences maintained at follow-up (intervention: 32.5±5.5 vs. control: 37.3±8.7 s; P=0.008). The intervention was associated with a speeding of the [HHb] τ (Pre: 20.1±4.7 vs. Post: 18.2±4.1 s; P=0.05), compared to a slowing over the same time period in the control participants (Pre: 17.9±4.9 vs. Post: 20.1±4.6 s; P=0.012). HR kinetics were not altered (Pre: 46.5±12.2 vs. Post: 47.7±11.1 s; P=0.98).

Conclusion: These findings highlight the potential utility of school-based HIIT as a strategy to enhance the $\dot{V}O_2$ kinetics of youth, regardless of the presence of asthma.

Key Words

Oxygen uptake; fitness; Commando Joe's; the x4a trial: eXercise for Asthma; intervention; youth

Introduction

Asthma, characterised by episodes of breathlessness, wheezing, coughing and chest tightness (1), is one of the most common chronic diseases, affecting 1 in 11 children within the UK (2). Whilst the occurrence, or fear of occurrence, of exercise-induced asthma has been found to be associated with low physical activity levels and poor cardiorespiratory fitness in those with asthma (3), the influence of asthma *per se* on cardiorespiratory fitness during adolescence remains equivocal. Indeed, whilst some studies reported a lower cardiorespiratory fitness relative to their healthy peers (4, 5), others found no difference (6, 7), with such discrepancies potentially related to the severity of asthma within the respective study populations.

In addition to the extensive, well-evidenced benefits of exercise in healthy populations, further health benefits may be elicited in those with asthma, such as reduced symptoms and improved control (8). Whilst numerous studies have implemented exercise interventions, the majority have focused on constant-intensity exercise training. However, it has been suggested that asthma symptoms may be triggered by continuous exercise (9), highlighting the potential utility of high-intensity interval training (HIIT), which involves repeated, short, intense bouts of exercise, interspersed with either rest or active recovery (10). Indeed, the intermittent nature of HIIT may facilitate a decrease in end expiratory lung volume during the resting phase (11), reducing the risk of an asthma attack. Nevertheless, little is known about the physiological effect of HIIT on asthma.

Although peak oxygen uptake ($\dot{V}O_2$) is widely considered the gold standard measure of aerobic fitness, its relevance and applicability to daily life is questionable (12). As such, the interpretation of previous studies investigating the influence of asthma on cardiorespiratory fitness is limited by their reliance on peak $\dot{V}O_2$. Indeed, sub-maximal fitness accrued through sporadic daily activity is arguably better assessed by $\dot{V}O_2$ kinetics which reflect the dynamic

$\dot{V}O_2$ response to an instantaneous change in the metabolic demand (13). The $\dot{V}O_2$ kinetic response is highly sensitive to both exercise training and disease in adults, although considerably less is known regarding the influence of such stimuli in youth populations. Specifically, whilst cross-sectional studies have found training to be associated with a faster $\dot{V}O_2$ τ_p (14, 15), a six-week HIIT intervention only speeded the τ_p in obese but not in normal weight children (16). This contrasts findings in adults, which have shown HIIT to be a potent stimulus to the dynamic $\dot{V}O_2$ response, even after as little as two sessions (17).

It is suggested that the determinants of the dynamic $\dot{V}O_2$ response are displaced by disease (12); the airway derangements associated with asthma may, therefore, hinder the response to exercise with respect to oxygen delivery and utilisation. Indeed, recent studies in respiratory disease found impaired $\dot{V}O_2$ kinetics in those with Emphysema and Idiopathic Pulmonary Fibrosis (18) and Cystic Fibrosis (19), compared with age-matched healthy counterparts. This may be attributable to an impaired oxygen delivery consequent to mismatched ventilation and gas exchange in the lung, causing a low arterial oxygen content (12).

Despite widespread interest in HIIT, little is known about the effect of HIIT in children or adolescents, and particularly its interaction with asthma. Therefore, the aim of this study was to investigate the influence of asthma and HIIT, and their interaction, on the dynamic $\dot{V}O_2$ response in adolescents. It was hypothesised that the participants with asthma would have slower $\dot{V}O_2$ kinetics than their healthy peers and that the HIIT intervention would increase the peak $\dot{V}O_2$ and speed the $\dot{V}O_2$ kinetics, irrespective of disease status.

Methods

Participants

Sixty-nine adolescents (39 boys, 13.6 ± 0.9 years; 36 with asthma, 21 boys; Table 1) were selected using stratified randomisation as a sub-sample from 616 participants involved in a larger randomised trial: The Exercise for Asthma with Commando Joes Trial (20). These groups were stratified by age, sex and condition (asthma/non-asthma) to provide a representative sample of the wider population. Participating schools (one intervention and one control) were randomly selected from fifteen schools initially invited to take part and were of similar socio-economic status according to the percentage of free school meals.

Asthma severity was assessed using the Global Initiative for Asthma guidelines (1) and classified according to the medication step required to achieve asthma control. Participants were excluded if they did not have stable asthma. Ethical approval was granted by the institutional research ethics committee (ref: 140515 and PG/2014/29). Parent/guardian and head teacher consent, as well as child assent, were obtained prior to participation.

Intervention

Participants within the intervention group were required to attend a HIIT intervention, three days a week for six months. The 30-minute intervention sessions consisted of a mixture of circuits and games-based activities informed by our formative work (21) and designed to elicit a heart rate of >90% heart rate maximum (HR_{max}), with a 1:1 exercise to rest ratio. Throughout each exercise session, participants' heart rate (HR) was continuously monitored (Activio AB, Stockholm, SWE) and individual encouragement provided to those not attaining the desired intensity. The intervention was delivered by a trained professional from Commando Joe's® (Manchester, UK).

Procedures

The intervention and control groups were assessed at four time-points: baseline, mid-intervention, post-intervention and at a three-month follow-up. Participants were asked to attend the laboratory at the same time of day (± 2 hrs) four times at each of the time-points, separated by a minimum of 24 hours, in a rested and fully hydrated state and at least two hours postprandial. All exercise tests were performed on an electromagnetically braked cycle ergometer (Ergoselect 200, Ergoline GmbH, Lindenstrasse, Germany), with seat and handlebar height adjusted for each participant, with these heights kept consistent for all visits within a time-point.

Anthropometrics

Stature and sitting stature were measured to the nearest 0.1 cm (Seca213, Hamburg, Germany) and body mass to the nearest 0.1 kg (Seca876, Hamburg, Germany). Maturity offset was estimated according to the equations of Mirwald et al. (22).

Incremental Test

On the first visit of each time-point, participants performed an incremental ramp test to volitional exhaustion to determine peak $\dot{V}O_2$ and the gas exchange threshold (GET). The ramp protocol consisted of three minutes of unloaded pedalling (0 W) followed immediately by an increased work rate at 12 - 24 $W \cdot min^{-1}$. Throughout the test, participants were asked to maintain a cadence of 75 ± 5 revolutions per minute. The peak $\dot{V}O_2$ was taken as the highest 10-second average attained prior to volitional exhaustion. The GET was determined using the V-slope method (23). The work rate that would elicit 40% of the difference between GET and peak $\dot{V}O_2$ (Δ40%; heavy-intensity) was subsequently determined, accounting for the mean response time for $\dot{V}O_2$ during ramp exercise.

Step Exercise Tests

The subsequent three visits on separate days at each time-point enabled the determination of $\dot{V}O_2$, HR and deoxyhaemoglobin kinetics using heavy-intensity constant work rate (CWR) exercise. Each CWR test comprised of six minutes with no external resistance followed by an abrupt transition to the target work rate, which was maintained for six minutes. The participants were asked to maintain a cadence of 75 ± 5 revolutions per minute throughout.

Measurements

Pulmonary ventilation (VE) and gas exchange were measured on a breath-by-breath basis (Jaeger Oxycon Mobile, Jaeger, Hoechberg, Germany) using a facemask with low dead-space (< 90 ml) connected via an impeller turbine assembly (Jaeger Triple V, Hoechberg, Germany). Gas analysers were calibrated prior to each test with gases of known concentrations and the turbine volume transducer was calibrated using a built-in function calibrated using a 3l syringe (Hans Rudolph, Kansas City, MO). The volume and concentration signals were time-aligned by accounting for the delay in capillary gas transit and analyser rise time (<80 ms), relative to the volume signal. The inspired and expired gas volumes and concentration signals were continuously sampled at 100 Hz. Electrocardiogram was recorded continuously at a sampling frequency of 250 Hz from which HR was derived (Physio Flow PF-05 Lab1, Manatec Biomedical, France).

The oxygenation status of the right *m.vastus lateralis* was also monitored during each CWR test using near-infrared spectroscopy (Portamon, Artinis Medical Systems, Netherlands). The Portamon device consisted of three light sources emitting two wavelengths (760 and 850 nm) and a photon detector. The reflected light was recorded continuously at 10 Hz and used to estimate the changes in the concentration of oxygenated, deoxygenated ([HHb]) and total haemoglobin and myoglobin. The Portamon device was placed at the mid-point of the muscle

using micropore tape (3M, Maplewood, MN); to minimise movement and the interference of extraneous light, a bandage was wrapped around the Portamon device and leg.

Data Analysis

To account for body size and its influence on peak $\dot{V}O_2$, analysis of covariance (ANCOVA) was used to determine the allometric relationship between peak $\dot{V}O_2$ and body mass using log transformed data. Common allometric exponents were confirmed and power function ratios ($Y/X^{-0.57}$) were computed.

$\dot{V}O_2$ Kinetic Analysis

Breath-by-breath $\dot{V}O_2$ responses were first examined using a 5-second moving average to identify and remove any errant breaths which were more than four standard deviations from the local mean, caused, for example, by coughing, swallowing, or sighing. Each transition was then interpolated to 1-second intervals, time-aligned to the start of exercise and averaged to produce a single response profile at each time-point. Each CWR profile was then corrected for baseline $\dot{V}O_2$ and a mono-exponential model applied (Equation 1):

Equation 1

$$Y_{(t)} = A_1(1 - e^{-(t-\delta_1)/\tau p_1})$$

where Y is the increase at time t above the baseline value (calculated as the mean of the first 45-seconds of the last minute of baseline pedalling). A_1, δ_1 and τ_{p1} are the primary component amplitude, time delay (which was allowed to vary freely), and time constant, respectively. Variables derived from the mono-exponential model (A_1, δ_1 and τ_{p1}) and their 95% confidence intervals were determined by least squares non-linear regression analysis (Graphpad Prism, Graphpad Software, San Diego, CA). A mono-exponential model was selected as it provided

a superior fit to a bi-exponential model. Purpose-designed custom software was then used to iteratively fit a single-exponential function to the $\dot{V}O_2$ data until the window encompassed the entire exercise response. The resulting τ_p were plotted against time to identify the point at which the τ_p consistently deviated from the previously "flat" profile, providing the start time of the slow component. The amplitude of the $\dot{V}O_2$ slow component was determined as the difference between the $\dot{V}O_2$ at end of primary component and at end exercise (t = 360) and presented in absolute terms and as a percentage of end exercise $\dot{V}O_2$. Finally, the mean response time (MRT) was calculated by fitting equation 2, from t = 0 to t = 360.

Equation 2

$$Y_{(t)} = A_1(1 - e^{-(t)/\tau_1})$$

[HHb] & HR Kinetics Analysis

The [HHb] and HR responses to the CWR tests were modelled using a mono-exponential function (equation 2). Each transition was interpolated to 1-second intervals, time-aligned to the start of exercise and averaged to produce a single response profile for each time-point.

The [HHb] data were baseline averaged, expressed as a percentage of end-exercise amplitude and then averaged into 5-second time bins. The [HHb] was subsequently modelled using Equation 1, with the time delay identified as the time after exercise onset at which [HHb] began a systematic increase above the nadir value. The mono-exponential function was fitted between the identified time delay and time at which end of primary component τ was identified by the mono-exponential model of the $\dot{V}O_2$ kinetics. The [HHb] time delay and time constant were subsequently summed to give the MRT.

The HR responses were modelled by both Equations 1 and 2, with Equation 1 subsequently selected as it was deemed the superior fit for 91% of the transitions (Graphpad Prism, Graphpad Software, San Diego, CA). The mono-exponential model with a time delay was fitted between t = 0 and t = 360.

Statistics

Data normality was initially assessed by the Shapiro-Wilk test. Subsequently, mixed linear regression models were used to determine the overall effects of time, group and asthma, and their interactions on the dynamic $\dot{V}O_2$, HR and [HHb] responses when controlling for age and sex. A random intercept was included in each model to account for the repeated measure nature of the data. Planned contrasts were used to identify the specific location of significant main effects or interactions. Pearson's correlation coefficients were used to investigate the degree of association between key variables.

All analyses were conducted according to an intention-to-treat and per protocol approach. For the per protocol analyses, inclusion required a minimum completion of 70% of the intervention sessions throughout the intervention. The statistical analyses were conducted using Stata v 13 (StataCorp LP, Texas, USA). All data are presented as means ± standard deviation (SD). Statistical significance was accepted as $P < 0.05$.

Results

Maturity, stature and body mass increased in all groups across all four time-points, with no differences between intervention and control groups or those with and without asthma (Table 1). Those with asthma in the intervention group were characterised as 87% with mild persistent and 13% with moderate or severe asthma; in the control group, those with asthma were

categorised as 77% and 23% mild and moderate or severe, respectively. This prevalence was similar in both the intention-to-treat and per protocol analyses. Throughout the intervention sessions, excluding warm-up and cool-down, but including recovery between high-intensity bouts, participants' mean HR and mean HR peak were 155 ± 16 and 189 ± 12 beats·minute^{-1}, respectively (78 ± 8% HR_{max} and 95 ± 6% HR_{max}). The HR exceeded the threshold of >90%HR_{max} an average of 24% of the total time.

There was no significant difference between the intervention and control groups or asthma and non-asthma participants at baseline (Table 2; Figure 1). The intervention was associated with a significant increase in both absolute and scaled peak $\dot{V}O_2$ at post-intervention, irrespective of asthma status, although this was not maintained at follow-up. In contrast, in the control group, there was no significant change from baseline at any time-point in peak $\dot{V}O_2$, irrespective of the method of expression.

There was a significant main effect of time and interaction between time and group on the primary component $\dot{V}O_2$ amplitude (Table 2). Specifically, the primary component amplitude was greater post-intervention and at follow-up, with this difference attributable to increases relative to baseline in the intervention, but not the control group. The linear mixed models showed a similar interaction between time and group for the $\dot{V}O_2$ τ_p, with no main effect for time, asthma or group. The planned contrasts revealed that the $\dot{V}O_2$ τ_p was significantly lower in the intervention than control group at post-intervention and follow-up, with the $\dot{V}O_2$ τ_p significantly slower in the control group only at follow-up than baseline (Figure 2). In contrast, whilst the $\dot{V}O_2$ MRT increased with time, with a slower MRT at post-intervention and follow-up than baseline or mid-intervention, there was no effect of the intervention or asthma status, or interaction between factors. A $\dot{V}O_2$ slow component was manifest in all participants; the

magnitude of the $\dot{V}O_2$ slow component increased in both absolute and relative terms across the intervention, with no main effect of asthma or group. A significant interaction between time and group was observed, with the $\dot{V}O_2$ slow component greater at post-intervention in both intervention and control groups and follow-up in the intervention group. However, this interaction was not significant according to the per protocol analyses. Similarly, in the intention-to-treat but not per protocol analyses, an interaction was observed between asthma and time, with the magnitude of the $\dot{V}O_2$ slow component increasing at each time-point in those with asthma only.

The mixed models and subsequent planned contrasts revealed similar effects in the [HHb] τ and MRT, with a significant main effect of time and interaction between time and group. Specifically, in the intervention group, the τ and MRT were significantly faster at the mid-intervention time-point, but not at the post-intervention ($P = 0.07$) or follow-up time-points (Table 3). In contrast, both the [HHb] τ and MRT significantly slowed throughout the intervention period in the control group. According to either the intention-to-treat or per protocol analyses, there was no significant effect of, or interaction between, time, asthma or group on the HR τ.

Irrespective of intention-to-treat or per protocol analyses, a significant effect of age and sex were manifest in the $\dot{V}O_2$ and HR, but not [HHb], response. Specifically, girls had a smaller $\dot{V}O_2$ primary component ($\beta = -0.33$ (-0.45 to -0.21) $l \cdot min^{-1}$; $P < 0.01$) and slow component amplitude ($\beta = -0.29$ (-0.51 to -0.07) $l \cdot min^{-1}$; $P = 0.007$) and slower $\dot{V}O_2$ τ_p ($\beta = 2.4$ (0.2 to 4.5) s; $P = 0.031$), MRT ($\beta = 3.8$ (0.6 to 6.9) s; $P = 0.020$) and HR τ than boys ($\beta = 9.0$ (4.5 to 13.5) s; $P < 0.01$). The $\dot{V}O_2$ primary component amplitude ($\beta = 0.13$ (0.06 to 0.20) $l \cdot min^{-1}$; $P < 0.01$)

and slow component amplitude (β = 0.25 (0.13 to 0.38) l·min^{-1}; P < 0.01) increased with age, whilst the $\dot{V}O_2$ MRT slowed (β = 2.5 (0.7 to 4.3); P = 0.006).

Discussion

This is the first study to investigate the influence of HIIT, asthma, or their interaction, on the dynamic $\dot{V}O_2$ response and its determinants. The primary findings of this study were that the six-month, school-based HIIT intervention was associated with a significantly faster primary component τ_p in the intervention than control participants. This change is most likely attributable to changes in peripheral oxygen extraction, as indicated by the faster [HHb] τ and MRT in the intervention participants, and not to central changes in bulk oxygen delivery which, according to the HR kinetics, appear to be unaffected by HIIT in youth. Importantly, asthma did not influence the aerobic fitness or response to HIIT, with a similar peak $\dot{V}O_2$ and $\dot{V}O_2$ τ_p, irrespective of asthma status. These findings highlight the potential utility of school-based HIIT as a strategy to enhance the aerobic fitness of youth, regardless of the presence of asthma.

Following the six-month intervention, HIIT was associated with a ~17% faster $\dot{V}O_2$ τ_p in the intervention participants in comparison to the controls, with this difference maintained at the three-month follow-up. Although smaller than the differences previously reported in cross-sectional comparisons of the dynamic $\dot{V}O_2$ response in trained and untrained youth (14, 24), this degree of change is greater than suggested following traditional endurance exercise in youth (25). It is also pertinent to note the time course of these adaptations, with no significant effect manifest at the mid-intervention time-point. This adaptation in $\dot{V}O_2$ kinetics is therefore considerably slower than typically reported in adults, where adaptations have been reported after as little as two days of training (17). However, this time course does appear to agree with

other studies in youth in which no effect of six-weeks high-intensity exercise was reported on the dynamic $\dot{V}O_2$ response of normal weight children (16). These findings may therefore suggest that longer intervention periods are required to elicit changes in the $\dot{V}O_2$ kinetic response, possibly indicating that the baseline fitness of youth is sufficient so that a greater intervention dose is required to engender significant improvements. Indeed, baseline fitness is well accepted to mediate the magnitude of change anticipated following an exercise intervention (26). Whilst further inter-study comparisons in youth are largely precluded by the different high-intensity exercise protocols used in each study, it is perhaps worth considering the potential role of maturity in these discrepancies. Specifically, it has previously been suggested that there may be a maturational threshold below which significant influences of training cannot be manifest (27). Given that the participants in McNarry et al. (16) were pre-pubertal and those in the current study were pubertal, this could be construed as those in the earlier study lacking trainability. However, as significant effects of training status on the $\dot{V}O_2$ kinetics of pre-pubertal children have previously been reported (28), and indeed, the overweight/obese participants in McNarry et al. (16) demonstrated a significantly faster $\dot{V}O_2$ τ_p, a maturity-related explanation seems implausible.

In contrast to cross-sectional studies which found both central and peripheral factors likely contributed to the faster $\dot{V}O_2$ kinetics in the trained youth (14, 24), the current findings suggest that six-months of HIIT is associated with peripheral, but not central, adaptations at the onset of exercise. Specifically, a faster [HHb] τ, a reflection of local fractional oxygen extraction within the exercising muscle (13), was observed at the three-months mid-intervention ($P < 0.05$), but not six-months ($P = 0.07$). In contrast, the HR τ, which may provide a crude estimate of bulk blood flow kinetics (29), was unchanged. These findings are therefore in accord with

304 the growing body of evidence that suggests that bulk O_2 delivery is not limited to $\dot{V}O_2$ kinetics
305 during upright exercise in healthy people (12).
306
307 The faster rate of oxygen extraction (faster [HHb]) in the current intervention participants is
308 most likely to be predominantly related to an enhanced oxidative capacity (30), although the
309 specific molecular and cellular adaptations that underpin this greater oxidative capacity,
310 particularly in youth populations, remains to be elucidated. Indeed, evidence regarding the
311 muscle oxidative capacity of youth, and the influence of training on it, remains almost non-
312 existent, with current conclusions reliant on evidence from more than 35 years ago which
313 indicated that (endurance) training elicits an increase in oxidative enzyme activity in boys (31,
314 32). Whether similar adaptations are manifest in response to HIIT in youth is unknown. The
315 faster $\dot{V}O_2$ kinetics in the intervention group may also reflect an altered proportion, or perhaps
316 more likely, recruitment of muscle fibre types following HIIT (33). However, HIIT would be
317 expected to predominantly engage more type II than type I muscle fibres during the exercises.
318 Therefore, an increased contribution of type I muscle fibres following training, as would be
319 required for muscle fibre type to partly explain the faster $\dot{V}O_2$ kinetics (34), is perhaps unlikely.
320 It is, however, possible that the training was associated with greater fatigue-resistance in the
321 type II fibres, which would therefore enable a greater net contribution of type I fibres following
322 the intervention.
323
324 When considering the mechanistic basis for the faster [HHb] τ and MRT, and their potential
325 contribution to the faster $\dot{V}O_2$ τ_p, it is worth noting the temporal dissociation in the time course
326 of adaptation of these parameters and their lack of correlation across the study period.
327 Specifically, whilst the [HHb] τ and MRT were both observed to be significantly faster in the
328 intervention than control group by three months, similar adaptation was not evident in the $\dot{V}O_2$

τ_p until six months. Interpretation of this dissociation is beyond the scope of this study but the earlier adaption of oxygen extraction than utilisation does not preclude a mechanistic link between these adaptations.

The magnitude of the $\dot{V}O_2$ slow component is typically reported to be attenuated following endurance training in adults (35, 36). However, the influence of HIIT remains equivocal, not least due to considerable discrepancies between studies in the definition and implementation of "HIIT", which largely precludes inter-study comparisons. In the only previous study to consider the influence of a HIIT intervention on the $\dot{V}O_2$ slow component response in youth (16), a similar lack of change in magnitude was observed as in the current study. The $\dot{V}O_2$ slow component is generally accepted to be predominantly related to factors intrinsic to the exercising muscles, including the recruitment of less efficient motor units, a reduced mechanical coupling efficiency and changes in the metabolic requirements of the fatiguing muscle fibres (12). The high-intensity bouts in the current HIIT protocol may therefore have been too short to elicit changes in these intrinsic factors or the use of the same relative, rather than absolute, intensity pre- and post-training may have precluded a significant effect from being observed.

When interpreting the current influence of HIIT it is important to consider the concomitant influences of age and sex. Specifically, time was associated with a significant slowing of the $\dot{V}O_2$ τ_p in the control participants, despite no changes in peak $\dot{V}O_2$. Similar time-related changes in the $\dot{V}O_2$ τ_p have previously been suggested to be associated with changes in the muscle phosphate controllers of oxidative phosphorylation and/or changes in muscle oxygen delivery and utilisation (37), which may be reflected by the slowing of the [HHb] and HR responses observed across the current study period. The slower $\dot{V}O_2$ τ_p, MRT and increased $\dot{V}O_2$ slow

component amplitude observed over the course of the current study in the control participants may also be related to changes in muscle fibre type recruitment patterns (33), with the progressive recruitment of muscle fibres during exercise becoming increasingly more important for meeting the exercise demand with age.

Few studies have specifically investigated the influence of sex on the $\dot{V}O_2$ kinetics response and, consequently, little consensus has been reached. In agreement with the limited evidence available (38, 39), girls demonstrated a slower $\dot{V}O_2$ τ_p and MRT in the current study but, contrary to these earlier studies, girls also demonstrated a smaller $\dot{V}O_2$ slow component amplitude, although this difference was abolished when the slow component was expressed relative to end exercise amplitude. The boys in the present study also demonstrated a faster HR τ, which was correlated with the $\dot{V}O_2$ τ_p (r = 0.31; P < 0.01); this could be indicative that girls are subject to a greater propensity for at least some degree of oxygen delivery limitation. However, this apparent sex-difference may also simply be a reflection of differences in aerobic fitness as peak $\dot{V}O_2$ was also higher in boys, irrespective of whether this was expressed in absolute or allometrically-scaled terms.

In contrast to our hypothesis and previous studies (6, 7), asthma did not affect peak $\dot{V}O_2$ or $\dot{V}O_2$ kineticresponses. Given that adolescents with other chronic airway conditions, such as Cystic Fibrosis, have been shown to have impaired $\dot{V}O_2$ kinetics (19), it was anticipated that this would also be manifest in adolescents with asthma. This lack of effect could have been due to the current participants being predominantly characterised as having mild asthma, which may have been insufficient for derangements to be manifest. It is perhaps pertinent to note, however, that even in those with mild asthma, a lower peak $\dot{V}O_2$ has previously been reported compared to their healthy age- and sex-matched counterparts (4). Alternatively, the lack of effect of asthma

379 may be due to the youth study population; the derangements typically reported in adults with
380 asthma may be related to a longer disease history and therefore were not yet manifest in our
381 participants. This highlights a potentially important interventional target: HIIT may represent
382 an effective tool to prevent the onset of derangements in aerobic fitness in those with asthma,
383 although further research that encompasses the age and disease severity spectrum are required
384 to investigate this further. Importantly, the current findings suggest that there is no
385 deconditioning effect of asthma on the aerobic fitness of adolescents.
386
387 A key strength of this study was the repeated transitions to determine the dynamic $\dot{V}O_2$, HR
388 and [HHb] responses at each time-point. This provides confidence in the results, with 95%
389 confidence intervals (mean ± SD seconds) well within those recommended by Fawkner and
390 Armstrong (40). Furthermore, this is the first study to consider the sustainability of HIIT-
391 induced training adaptations through a three-month follow-up. Nonetheless, the study is not
392 without its limitations. Specifically, it is not possible to preclude the potential for a self-
393 selection bias, whereby adolescents that enjoyed and already engaged in exercise were more
394 likely to participate. However, the baseline peak $\dot{V}O_2$ of the current participants does not
395 suggest they were highly active or trained, with a peak $\dot{V}O_2$ that was equivalent to that reported
396 elsewhere in untrained youth. The inclusion of age- and sex-matched controls accounted for
397 the concomitant effects of growth and maturation that could have masked or confounded the
398 interpretation of the effect of HIIT, but the relatively poor adherence to the protocol throughout
399 the six-month period perhaps questions its real-world applicability, despite its efficacy. Further
400 research is required that considers the minimum dose of HIIT required to elicit favourable
401 physiological adaptations, which may be more tolerable as a long-term exercise strategy for
402 youth. Furthermore, to advance our understanding of the mechanistic basis of the observed
403 changes in the dynamic $\dot{V}O_2$ response following training, future studies should consider using

muscle occlusion protocols to investigate oxidative capacity and more direct estimates of muscle blood flow.

In conclusion, six-months of school-based HIIT was associated with a significantly faster $\dot{V}O_2\tau_p$ in the intervention than control participants, most likely due to changes in peripheral oxygen extraction, as indicated by the faster [HHb] τ and MRT in the intervention participants. Importantly, no effect of asthma was evident on the aerobic fitness of youth or the response to HIIT. These findings highlight the potential utility of school-based HIIT as a strategy to enhance the aerobic fitness of youth, regardless of the presence of asthma.

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Conflicts of Interest and Source of Funding

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Figure 1. Pulmonary oxygen uptake response to the onset of heavy intensity constant work rate exercise in a representative participant with (closed circles) and without (open circles) asthma at baseline.

Figure 2. Pulmonary oxygen uptake response to the onset of heavy intensity constant work rate exercise in a representative A) intervention and B) control participant at baseline (closed circles) and post-intervention (open circles).