

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

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4 ¹McNarry MA, ^{1,2}Winn CON, ²Davies GA, ¹Eddolls WTB, ¹Mackintosh KA

5
6 ¹ Applied Sports Technology, Exercise and Medicine (A-STEM) Research Centre, College of
7 Engineering, Bay Campus, Swansea University, Swansea, SA1 8EN, UK

8
9 ² Swansea University Medical School, Singleton Campus, Swansea University, Swansea,
10 SA2 8PP, UK

11
12 Corresponding Author: Melitta McNarry, m.mcnarry@swansea.ac.uk, +44 (0)1792 513069

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

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16 **ORCHID ID**

17 Melitta McNarry: 0000-0003-0813-7477

18 Charles Winn: 0000-0001-8769-2764

19 Gwyneth Davies: 0000-0003-1218-1008

20 William Eddolls: 0000-0002-9590-8817

21 Kelly Mackintosh: 0000-0003-0355-6357

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

22 **Introduction**

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

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

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

46 $\dot{V}O_2$ response to an instantaneous change in the metabolic demand (13). The $\dot{V}O_2$ kinetic
47 response is highly sensitive to both exercise training and disease in adults, although
48 considerably less is known regarding the influence of such stimuli in youth populations.
49 Specifically, whilst cross-sectional studies have found training to be associated with a faster
50 $\dot{V}O_2 \tau_p$ (14, 15), a six-week HIIT intervention only speeded the τ_p in obese but not in normal
51 weight children (16). This contrasts findings in adults, which have shown HIIT to be a potent
52 stimulus to the dynamic $\dot{V}O_2$ response, even after as little as two sessions (17).

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

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

66 **Methods**

67 **Participants**

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

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

80 **Intervention**

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

89 **Procedures**

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

98 *Anthropometrics*

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

102 *Incremental Test*

103 On the first visit of each time-point, participants performed an incremental ramp test to
104 volitional exhaustion to determine peak $\dot{V}O_2$ and the gas exchange threshold (GET). The ramp
105 protocol consisted of three minutes of unloaded pedalling (0 W) followed immediately by an
106 increased work rate at 12 - 24 W \cdot min⁻¹. Throughout the test, participants were asked to maintain
107 a cadence of 75 ± 5 revolutions per minute. The peak $\dot{V}O_2$ was taken as the highest 10-second
108 average attained prior to volitional exhaustion. The GET was determined using the V-slope
109 method (23). The work rate that would elicit 40% of the difference between GET and peak
110 $\dot{V}O_2$ ($\Delta 40\%$; heavy-intensity) was subsequently determined, accounting for the mean response
111 time for $\dot{V}O_2$ during ramp exercise.

112 *Step Exercise Tests*

113 The subsequent three visits on separate days at each time-point enabled the determination of
114 $\dot{V}O_2$, HR and deoxyhaemoglobin kinetics using heavy-intensity constant work rate (CWR)
115 exercise. Each CWR test comprised of six minutes with no external resistance followed by an
116 abrupt transition to the target work rate, which was maintained for six minutes. The participants
117 were asked to maintain a cadence of 75 ± 5 revolutions per minute throughout.

118 **Measurements**

119 Pulmonary ventilation (VE) and gas exchange were measured on a breath-by-breath basis
120 (Jaeger Oxycon Mobile, Jaeger, Hoechberg, Germany) using a facemask with low dead-space
121 (< 90 ml) connected via an impeller turbine assembly (Jaeger Triple V, Hoechberg, Germany).
122 Gas analysers were calibrated prior to each test with gases of known concentrations and the
123 turbine volume transducer was calibrated using a built-in function calibrated using a 3l syringe
124 (Hans Rudolph, Kansas City, MO). The volume and concentration signals were time-aligned
125 by accounting for the delay in capillary gas transit and analyser rise time (<80 ms), relative to
126 the volume signal. The inspired and expired gas volumes and concentration signals were
127 continuously sampled at 100 Hz. Electrocardiogram was recorded continuously at a sampling
128 frequency of 250 Hz from which HR was derived (Physio Flow PF-05 Lab1, Manatec
129 Biomedical, France).

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

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

138 **Data Analysis**

139 To account for body size and its influence on peak $\dot{V}O_2$, analysis of covariance (ANCOVA)
140 was used to determine the allometric relationship between peak $\dot{V}O_2$ and body mass using log
141 transformed data. Common allometric exponents were confirmed and power function ratios
142 $(Y/X^{-0.57})$ were computed.

143 *$\dot{V}O_2$ Kinetic Analysis*

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

150

151 Equation 1

$$152 \quad Y_{(t)} = A_1(1 - e^{-(t-\delta_1)/\tau_{p1}})$$

153

154 where Y is the increase at time t above the baseline value (calculated as the mean of the first
155 45-seconds of the last minute of baseline pedalling). A_1 , δ_1 and τ_{p1} are the primary component
156 amplitude, time delay (which was allowed to vary freely), and time constant, respectively.
157 Variables derived from the mono-exponential model (A_1 , δ_1 and τ_{p1}) and their 95% confidence
158 intervals were determined by least squares non-linear regression analysis (Graphpad Prism,
159 Graphpad Software, San Diego, CA). A mono-exponential model was selected as it provided

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

168

169 Equation 2

$$170 \quad Y_{(t)} = A_1(1 - e^{-(t)/\tau_1})$$

171

172 *[HHb] & HR Kinetics Analysis*

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

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

183

184 The HR responses were modelled by both Equations 1 and 2, with Equation 1 subsequently
185 selected as it was deemed the superior fit for 91% of the transitions (Graphpad Prism, Graphpad
186 Software, San Diego, CA). The mono-exponential model with a time delay was fitted between
187 $t = 0$ and $t = 360$.

188 **Statistics**

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

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

201

202 **Results**

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

207 categorised as 77% and 23% mild and moderate or severe, respectively. This prevalence was
208 similar in both the intention-to-treat and per protocol analyses. Throughout the intervention
209 sessions, excluding warm-up and cool-down, but including recovery between high-intensity
210 bouts, participants' mean HR and mean HR peak were 155 ± 16 and 189 ± 12 beats·minute⁻¹,
211 respectively ($78 \pm 8\%$ HR_{max} and $95 \pm 6\%$ HR_{max}). The HR exceeded the threshold of
212 $>90\%$ HR_{max} an average of 24% of the total time.

213

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

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

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

239

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

248

249 Irrespective of intention-to-treat or per protocol analyses, a significant effect of age and sex
250 were manifest in the $\dot{V}O_2$ and HR, but not [HHb], response. Specifically, girls had a smaller
251 $\dot{V}O_2$ primary component ($\beta = -0.33$ (-0.45 to -0.21) $l \cdot \text{min}^{-1}$; $P < 0.01$) and slow component
252 amplitude ($\beta = -0.29$ (-0.51 to -0.07) $l \cdot \text{min}^{-1}$; $P = 0.007$) and slower $\dot{V}O_2$ τ_p ($\beta = 2.4$ (0.2 to 4.5)
253 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)
254 s; $P < 0.01$). The $\dot{V}O_2$ primary component amplitude ($\beta = 0.13$ (0.06 to 0.20) $l \cdot \text{min}^{-1}$; $P < 0.01$)

255 and slow component amplitude ($\beta = 0.25$ (0.13 to 0.38) $\text{l}\cdot\text{min}^{-1}$; $P < 0.01$) increased with age,
256 whilst the $\dot{V}\text{O}_2$ MRT slowed ($\beta = 2.5$ (0.7 to 4.3); $P = 0.006$).

257

258

259 **Discussion**

260 This is the first study to investigate the influence of HIIT, asthma, or their interaction, on the
261 dynamic $\dot{V}\text{O}_2$ response and its determinants. The primary findings of this study were that the
262 six-month, school-based HIIT intervention was associated with a significantly faster primary
263 component τ_p in the intervention than control participants. This change is most likely
264 attributable to changes in peripheral oxygen extraction, as indicated by the faster [HHb] τ and
265 MRT in the intervention participants, and not to central changes in bulk oxygen delivery which,
266 according to the HR kinetics, appear to be unaffected by HIIT in youth. Importantly, asthma
267 did not influence the aerobic fitness or response to HIIT, with a similar peak $\dot{V}\text{O}_2$ and $\dot{V}\text{O}_2 \tau_p$,
268 irrespective of asthma status. These findings highlight the potential utility of school-based HIIT
269 as a strategy to enhance the aerobic fitness of youth, regardless of the presence of asthma.

270

271 Following the six-month intervention, HIIT was associated with a ~17% faster $\dot{V}\text{O}_2 \tau_p$ in the
272 intervention participants in comparison to the controls, with this difference maintained at the
273 three-month follow-up. Although smaller than the differences previously reported in cross-
274 sectional comparisons of the dynamic $\dot{V}\text{O}_2$ response in trained and untrained youth (14, 24),
275 this degree of change is greater than suggested following traditional endurance exercise in
276 youth (25). It is also pertinent to note the time course of these adaptations, with no significant
277 effect manifest at the mid-intervention time-point. This adaptation in $\dot{V}\text{O}_2$ kinetics is therefore
278 considerably slower than typically reported in adults, where adaptations have been reported
279 after as little as two days of training (17). However, this time course does appear to agree with

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

296

297 In contrast to cross-sectional studies which found both central and peripheral factors likely
298 contributed to the faster $\dot{V}O_2$ kinetics in the trained youth (14, 24), the current findings suggest
299 that six-months of HIIT is associated with peripheral, but not central, adaptations at the onset
300 of exercise. Specifically, a faster [HHb] τ , a reflection of local fractional oxygen extraction
301 within the exercising muscle (13), was observed at the three-months mid-intervention ($P <$
302 0.05), but not six-months ($P = 0.07$). In contrast, the HR τ , which may provide a crude estimate
303 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 O₂ 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 $\dot{V}O_2$

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

332

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

346

347 When interpreting the current influence of HIIT it is important to consider the concomitant
348 influences of age and sex. Specifically, time was associated with a significant slowing of the
349 $\dot{V}O_2 \tau_p$ in the control participants, despite no changes in peak $\dot{V}O_2$. Similar time-related changes
350 in the $\dot{V}O_2 \tau_p$ have previously been suggested to be associated with changes in the muscle
351 phosphate controllers of oxidative phosphorylation and/or changes in muscle oxygen delivery
352 and utilisation (37), which may be reflected by the slowing of the [HHb] and HR responses
353 observed across the current study period. The slower $\dot{V}O_2 \tau_p$, MRT and increased $\dot{V}O_2$ slow

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

358

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

370

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

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

406

407 In conclusion, six-months of school-based HIIT was associated with a significantly faster $\dot{V}O_{2\tau p}$
408 in the intervention than control participants, most likely due to changes in peripheral oxygen
409 extraction, as indicated by the faster [HHb] τ and MRT in the intervention participants.
410 Importantly, no effect of asthma was evident on the aerobic fitness of youth or the response to
411 HIIT. These findings highlight the potential utility of school-based HIIT as a strategy to
412 enhance the aerobic fitness of youth, regardless of the presence of asthma.

413

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422

423

424 **Conflicts of Interest and Source of Funding**

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428

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514

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

518

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