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Effect of Asthma and Six-Months High-Intensity Interval Training on Heart Rate Variability during Exercise in Adolescents

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Abstract

Little is known regarding the influence of asthma and exercise, and their interaction, on heart rate variability in adolescents.

Thirty-one adolescents with asthma (13.7±0.9 years; 21.9±3.9 kg·m^{-2}; 19 boys, 12 girls) and thirty-three healthy adolescents (13.8±0.9 years; 20.3±3.2 kg·m^{-2}; 16 boys, 17 girls) completed an incremental ramp test and three heavy-intensity constant-work-rate cycle tests. Thirteen adolescents (7 boys, 6 girls; 6 asthma, 7 control) completed six-months high-intensity interval training (HIIT) and were compared to age- and sex-matched controls. Standard time-domain, frequency-domain and non-linear indices of heart rate variability (HRV) were derived at baseline, three- and six-months.

Asthma did not influence HRV at baseline or following HIIT. Total power, low frequency and normalised low frequency power, and sympathovagal balance increased at three-months in HIIT, subsequently declining towards baseline at six-months. Normalised high frequency power was reduced at three-months in both groups, which was sustained at six-months. No effects of HIIT were observed in the time-domain nor in the non-linear indices.

HRV was not influenced by asthma, potentially because such derangements are a function of disease progression, severity or duration. HIIT may be associated with a short-term shift towards greater sympathetic predominance during exercise, perhaps caused by physiological overload and fatigue.

Keywords: Heart rate variability; Youth; Exercise; Non-linear; Children

Introduction

Heart rate variability (HRV) provides a non-invasive insight into the function of the autonomic nervous system (TaskForce, 1996) by measuring changes in beat-to-beat variability of the cardiac (RR) interval. Indeed, an altered HRV has been associated with a multitude of pathological conditions, including respiratory conditions such as Chronic Obstructive Pulmonary Disease and Cystic Fibrosis (e.g. Chang, Silberstein, Rambod, Porszasz, & Casaburi, 2011; McNarry & Mackintosh, 2016).

Asthma, a chronic respiratory condition characterised by swelling of the bronchioles that leads to breathlessness and wheezing (Carson et al., 2013), is one of the most common respiratory diseases in the world affecting approximately 1 in 11 children (Wanrooij, Willeboordse, Dompeling, & van de Kant, 2014). In adults, it is generally accepted that asthma is associated with cardiac parasympathetic predominance (Lutfi, 2012, 2015), the degree of which is associated with asthma severity (Lutfi, 2012). However, it is unclear whether the same is true in youth with asthma, since some studies have reported a similar parasympathetic predominance (Emin et al., 2012; Fujii et al., 2000; Gomes et al., 2013; Ostrowska-Nawarycz, Wroński, Błaszczyk, Buczyłko, & Nawarycz, 2006), yet others have found no influence of asthma on parasympathetic modulation (Rezvan, Dabidi Roshan, & Mahmudi, 2015). These discrepancies might be related to methodological limitations which preclude inter-study comparisons, such as the inclusion of obese participants (Rezvan, et al., 2015), a wide range of participant ages with no consideration of maturational status (Emin, et al., 2012; Fujii, et al., 2000; Ostrowska-Nawarycz, et al., 2006) or the use of absolute exercise intensities (Astrup et al., 2007; Galinier et al., 2000; Ostrowska-Nawarycz, et al., 2006). Indeed, a reliance on absolute work rates fails to account for inter-participant

differences in relative exercise intensities and the metabolic cost they engender. Since characteristic changes in HRV with increasing exercise effort are well documented (Lewis, Kingsley, Short, & Simpson, 2007), a reliance on absolute work rates might confound any interpretation of differences in HRV during or following exercise. It should also be noted that Rezvan et al. (2015) quantified HRV *during* exercise, whilst most others examined it pre to post. Indeed, given that autonomic dysfunction has been suggested to be associated with the pathologic response to exercise in those with asthma (Lewis, Short, & Lewis, 2006), further research comparing HRV during exercise in youth with asthma and their healthy counterparts is warranted.

Exercise is associated with improved lung function and mental health in those with asthma (Avallone & McLeish, 2013), as well as helping to prevent , or at least reduce the symptoms of asthma (Andrade, Britto, Lucena-Silva, Gomes, & Figueroa, 2014; Westergren et al., 2016). Furthermore, adults with asthma who engage in higher levels of moderate-to-vigorous physical activity demonstrate a similar HRV to healthy adults (Yueh- Shia, Fu-Chih, Su- Ru, & Chii, 2011). However, no studies have investigated whether HRV dysfunction is influenced by exercise in adolescents with asthma.

A commonly cited barrier for those with asthma is a fear of exercise-induced bronchoconstriction (Carson, et al., 2013), which is more likely to occur during continuous aerobic exercise (Sidiropoulou, Fotiadou, Tsimaras, Zakas, & Angelopoulou, 2007). In contrast, intermittent exercise places a lower burden on the respiratory system (Beauchamp et al., 2010), suggesting that high-intensity interval training (HIIT) has potential as an exercise modality to help manage asthma. Indeed, in adults, HIIT has been more effective than aerobic endurance training at eliciting improvements in HRV (Heydari, Boutcher, &

Boutcher, 2013; Kiviniemi et al., 2014) although similar studies have produced no effects in children, despite significant increases in aerobic fitness (Mandigout *et al.* (2002) and Gamelin *et al*. (2009)) . The reasons for these discrepancies are unclear and further research is required to elucidate whether they reflect physiological or methodological differences.

Therefore, the purpose of this study was to investigate the influences of asthma and HIIT, and their interaction, on the HRV of adolescents during exercise of a relative exercise intensity. It was hypothesised that individuals with asthma would have a parasympathetic predominance and reduced total HRV during light- and heavy-intensity exercise, and that these differences would be ameliorated by the intervention.

Methods

Participants

Sixty-four adolescents (35 boys, 29 girls; 13.7 ± 0.9 years) were selected using stratified randomisation from 618 participants who were involved in a larger randomised control trial (The X4A trial: eXercise for Asthma with Commando Joe's). This sample included thirty-one adolescents with asthma (13.7±0.9 years; 19 boys, 12 girls) and thirty-three healthy adolescents (13.8±0.9 years; 16 boys, 17 girls). Asthma severity was assessed using the Global Initiative for Asthma guidelines (Global Initiative for Asthma, 2017) according to the medication step required to achieve asthma control and classified the current participants as having mild (n = 27) or severe (n = 4) asthma. 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 consent and child assent were obtained prior to participation.

Intervention

The intervention design was based on formative work (Winn et al., 2017). Participants within the intervention group were required to attend a six-month HIIT intervention, three days per week, in accord with recommendations from recent systematic reviews (Eddolls, McNarry, Stratton, Winn, & Mackintosh, 2017). The 30-minute sessions consisted of circuits and games-based activities designed to elicit a heart rate of >90% Heart Rate maximum (HR_{max}) derived during the incremental ramp exercise test, with a 1:1 exercise to rest ratio. The duration of the bouts was progressively increased from 10 s bouts initially to 30 s bouts. Throughout each session, participants' HRs were continuously monitored (Activio AB, Stockholm, SWE). Maximal HR was predicted using the formula of Tanaka et al. (2001), validated for use in adolescents (Mahon, Marjerrison, Lee, Woodruff, & Hanna, 2010). The intervention was delivered by a trained professional from Commando Joe's® (Manchester, UK). Participants in the control group engaged in their usual day-to-day activities.

Procedures

Participants were assessed at three time-points: baseline, mid-intervention (3-months), and post-intervention. Each participant was asked to attend the laboratory at the same time during the school day (± 2 hrs), in a hydrated state and at least two hours postprandial. All the exercise tests were performed on an electromagnetically braked cycle ergometer (Ergoselect 200, Ergoline GmbH, Lindenstrasse, Germany) and participants were asked to maintain a cadence of 75 ± 5 revolutions per minute.

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). Lower limb length was calculated as the difference between stature and sitting stature and subsequently used to estimate maturity offset using the equations of Mirwald et al. (2002).

Spirometry

Forced Expiratory Volume in 1 second (FEV_1) was measured using a portable dry spirometer (Vitalograph, Buckingham, UK). The best of three measurements was taken according to the American Thoracic Society Guidelines (2005) and expressed as a percentage of the age-sex-stature predicted value (Rosenthal et al., 1993).

Physical Activity

Participants wore the ActiGraph GT3X+ accelerometer (ActiGraph, Pensacola, Florida, USA), set at 100 Hz, on their right mid-axillary line at the level of the iliac crest for seven consecutive full days, only removing it if they undertook contact or water-based activities. Wear-time diaries were used to log the reasons and duration of accelerometer removal.

Incremental Test

On the first visit, participants performed an incremental ramp test to volitional exhaustion to determine peak oxygen uptake ($\dot{V}O_2$) and the Gas Exchange Threshold (GET). The ramp protocol consisted of 3 minutes of unloaded pedalling (0 W) followed immediately by an increase in work rate at 12-24 $W \cdot min^{-1}$. Peak $\dot{V}O_2$ was taken as the highest 10-second

157 average. The GET was determined using the V-slope method (Beaver, Wasserman, &
158 Whipp, 1986) and the work rate that would elicit 40% of the difference between GET and
159 peak $\dot{V}O_2$ (Δ40%) subsequently determined, accounting for the mean response time for $\dot{V}O_2$
160 during ramp incremental exercise (Whipp, Davis, Torres, & Wasserman, 1981).

161 ***Square Wave Exercise Tests***

162 Participants repeated three square-wave exercise transitions on separate days, at least 24
163 hours apart, which comprised of six minutes baseline pedalling against no external work
164 rate (0W, "light intensity exercise") followed by an abrupt transition to the target work rate
165 (Δ40%) which was maintained for six minutes.

166 ***Measurements***

167 Pulmonary ventilation (VE) and gas exchange ($\dot{V}O_2$ and $\dot{V}CO_2$) were measured on a breath-
168 by-breath basis (Jaeger Oxycon Mobile, Jaeger, Germany) using a facemask with low dead-
169 space connected via an impeller turbine assembly (Jaeger Triple V, Germany). Gas
170 analysers were calibrated prior to each test with gases of known concentrations and the
171 turbine volume transducer was calibrated using a built-in function calibrated using a 3l
172 syringe (Hans Rudolph, Kansas City, MO). The volume and concentration signals were
173 time-aligned by accounting for the delay in capillary gas transit and analyser rise time
174 relative to the volume signal.

175 Beat-to-beat RR intervals were recorded continuously by a six-lead
176 electrocardiogram (Physio Flow PF-05 Lab1, Manatec Biomedical, France) at a sampling
177 frequency of 250 Hz. The electrodes were positioned on the forehead, neck, xiphoid process

and on the left-hand side of the lower ribs, avoiding the abdominal muscles (Welsman, Bywater, Farr, Welford, & Armstrong, 2005).

Data analysis

Using a MATLAB-based package developed by Physioflow, the ECG recording from each constant-work-rate test was extracted and reformatted before using an independent software package (Kubios HRV 2.1, Biomedical Signal Analysis Group, Finland) to detect R-wave peaks from the ECG signal. The new signal was manually inspected for signal degradation and physiological artefacts. This was then verified by automatic processes in the software, ensuring removal of irregularly occurring large artefacts from the RR data prior to further analysis without significantly affecting the spectral components of interest (<1% of RR intervals were recorded as artefacts via both inspection techniques).

HRV variables from the final three minutes of each stage of exercise (unloaded and Δ40%) were quantified in the time domain (RMSSDRR: square root of the mean of the sum of the squares of differences between adjacent RR intervals; SDNN: standard deviation of all 'normal' RR intervals) according to the Task Force guidelines (1996). Frequency domain and non-linear measures of HRV were also derived. Specifically, prior to spectral analysis, RR interval data were re-sampled at 3.0 Hz to account for the mean HR_{max} during exercise (168 beats·min^{-1} being equivalent to 2.80 Hz) and to remove non-uniformly spaced RR intervals. Using Welch's periodogram method, re-sampled data were then linearly de-trended and segmented into consecutive 90 s Hamming windows, with a 50% overlap. This was designed to reduce spectral leakage before power spectral density was estimated using a fast Fourier transform algorithm. Data are presented as low-frequency (LF) power (0.04-

0.15 Hz), high-frequency (HF) power (0.15-0.40 Hz) and total power (TP; 0.01-0.40 Hz). In addition, extended frequency bandwidths are presented for HF and TP (HF_{Bf} and TP_{Bf}, respectively) to account for the high breathing frequencies (*Bf*) and RSA influences during exercise (Lewis *et al.*, 2007), with the upper limit relative to individual tests (*Bf* Hz = peak breathing frequency/60). LF, HF, and HF_{Bf} were also presented in normalised units (nu) and as ratios (LF/HF; LF/HF_{Bf}), acting as indicators of sympathovagal balance. Non-linear measures included the standard deviations of the Poincaré plot (SD1 and SD2). Additionally, sample entropy (SampEn), the quantified rate of entropy within the RR data sample, was derived, providing measures of signal complexity. The embedding dimension for this was set at $m = 2$ and tolerance at $r = 0.25 * SDNN$. Finally, de-trended fluctuation analysis was used to estimate the self-similarity within short- ($DFA\alpha1$ = 4-16 beats) and long-term ($DFA\alpha2$ = 16-64 beats) HRV indices.

The physical activity data was analysed using KineSoft (version 3.3.67; KineSoft, Saskatchewan, Canada) employing 1 second epochs with sustained periods of at least 20 minutes at zero counts considered non-wear-time (Catellier et al., 2005). A minimum daily wear-time of 10 hours for 3 days, including 1 weekend day, was selected in order to provide a more accurate overview of participants' habitual physical activity levels (Rich et al., 2013). Evenson, Catellier, Gill, Ondrak and McMurray (2008). Cut-points, shown to be valid and reliable determinants of physical activity intensity in children and adolescents (Trost, Loprinzi, Moore, & Pfeiffer, 2011), were used to calculate time spent in the different intensities.

Statistical Analysis

Individuals with moderate, mild and severe asthma were grouped since no differences between study variables were observed according to asthma severity. On completion of the intervention, 13 participants (7 healthy, 6 asthma (4 mild, 2 severe); 7 boys, 6 girls) met the criteria of providing a complete dataset and having attended at least two sessions per week for at least 70% of the intervention. This sub-sample of participants were therefore used for the analysis of the effect of the HIIT intervention, along with 13 age- and sex-matched controls (Table 2). This sub-sample did not differ anthropometrically from the wider study population.

Normal distribution was confirmed using the Shapiro-Wilks test. Subsequently, a mixed repeated measures ANOVA was conducted to investigate the influence of the intervention and its interaction with asthma status, with post-hoc analyses using a Bonferroni correction to identify the specific location of significant differences when a main effect was observed. All statistical analyses were computed using SPSS Statistics 22 (IBM Corp, Armonk, NY, 2013). Data are expressed as mean ± SD and statistical significance was accepted at $P \leq 0.05$.

Results

Baseline comparisons showed no significant anthropometric differences according to asthma status (Table 1) or between intervention and control groups (Table 2). Over the training period, both intervention and control groups demonstrated a (non-significant) upward trend for $\dot{V}O_{2peak}$ from baseline to three-months, with the intervention group demonstrating a further significant increase at six-months (2.02 ± 0.11 to 2.36 ± 0.14 l·min^{-}

243 [1], $P < 0.001$). Participants with asthma did not differ from their healthy peers in terms of the
244 HRV parameters at baseline or in response to the intervention. Subsequently, the asthma
245 and non-asthma groups were combined for further analyses to increase the statistical power
246 for assessing the effect of intervention.

247 ***Influence of HIIT on HRV during light-intensity exercise***

248 During light-intensity unloaded exercise, SDNN differed across time-points, with a
249 significant time by group interaction. Specifically, as presented in Table 3, in contrast to a
250 significant reduction in SDNN from baseline to three-months in the control group, SDNN
251 increased in the intervention group over the same period. A similar significant time by
252 group interaction was found for SD2, which increased at all time-points relative to baseline
253 in the intervention group (Table 3), but decreased from baseline to three-months in the
254 control group before returning to baseline at six-months.

255 ***Influence of HIIT on HRV during heavy-intensity exercise***

256 As shown in Table 4, the six-month HIIT intervention was associated with significant
257 alterations in frequency-domain HRV during the constant work rate, heavy-intensity
258 exercise, although no significant differences were observed in the time-domain or non-linear
259 measures. Specifically, in the intervention group, total power, low-frequency, normalised
260 LF and indices of sympathovagal balance demonstrated a significant time by group
261 interaction, increasing at three-months in the intervention group before declining towards
262 baseline values at six-months (Table 3). In the control group, indices of sympathovagal
263 balance were significantly reduced at three- and six-months compared to baseline. In

contrast, HFnu was significantly reduced at three- and six-months in the intervention group compared to an increased HFnu at six-months in the control group.

Discussion

The present study is the first to investigate the influence of asthma on ANS function in adolescents during relative intensity exercise and whether a six-month HIIT programme can ameliorate the any deleterious influences of asthma on HRV. In contrast to our hypotheses, HRV was not influenced by asthma and, despite eliciting a significant increase in aerobic fitness, the intervention did not influence HRV. Specifically, whilst no significant changes were observed in time-domain or non-linear measures, the spectral parameters, which are related, at least in part, to sympathetic activity, demonstrated significant training effects.

In adults with asthma, airway inflammation due to hyper-reactivity in response to certain stimuli, such as exercise, is associated, amongst other factors, with an abnormal ANS control, manifest in the form of a parasympathetic predominance associated with a reduced global HRV and tonic bronchoconstriction (Lewis, et al., 2006). However, while some authors report similar derangements in children with asthma at rest (Emin, et al., 2012; Ostrowska-Nawarycz, et al., 2006), differences during exercise are presently equivocal, with a lack of research in this area despite the potential importance and prognostic value of identifying altered ANS control in children and adolescents with asthma. In contrast to the present study, two studies have reported similar findings to those in adults (Fujii, et al., 2000; Gomes, et al., 2013), suggesting an increased vagal tone following exercise. However, in agreement with the current results, the most recent study by

Rezvan and colleagues (2015) found no difference in parasympathetic tone between those with and without asthma during and following incremental exercise, although they did report a greater reduction in HRV immediately post-exercise in those with asthma. The interpretation of these findings is limited by a number of methodological factors, such as the added confounder of using obese children in the study by Rezvan et al. (2015), which could be associated with independent influences on the ANS (Thayer, Yamamoto, & Brosschot, 2010), as well as a failure to use relative exercise intensities (Fujii, et al., 2000; Gomes, et al., 2013; Rezvan, et al., 2015). The use of relative exercise intensities is important because increasing intensity is associated with a global reduction in HRV (Lewis, et al., 2007; Perini & Veicsteinas, 2003). Therefore, if participants are not exercising at the same relative intensity, erroneous conclusions could be drawn regarding HRV which are really a reflection of different exercise intensities, rather than disease related differences *per se* between groups. Finally, all of the studies to date have involved pre-pubertal children and therefore do not account for the potential influence of maturity on the ANS (Lenard, Studinger, Mersich, Kocsis, & Kollai, 2004), or for the interaction between these maturity-related adaptations and the influence of asthma. These methodological differences might explain the discrepant findings of the present study, which suggest that asthma does not influence ANS control during exercise in pubertal adolescents, although it is pertinent that previous studies have largely focussed on HRV following exercise (Emin, et al., 2012; Fujii, et al., 2000; Gomes, et al., 2013; Ostrowska-Nawarycz, et al., 2006), thereby limiting comparisons. It is also important to consider the potential interaction between disease severity and ANS control as the relatively mild, self-reported, severity of asthma in the present participants may have been insufficient to elicit significant derangements in ANS

control. Alternatively, the discrepancy between the present results and those in adults may reflect disease progression or longevity such that alterations in ANS control are not manifest until adulthood. Indeed, the degree of autonomic derangement is related to asthma duration (Lutfi, 2012), as well as medication use. Specifically, participants with asthma severe enough to potentially induce significant changes in sympathovagal tone were likely to be medicated with either, or both, short- and long-acting beta-agonists. Lewis et al. (2006) found that these medications increased cardiac sympathetic excitement and could explain the appearance of similar sympathovagal balances between those with and without asthma. Whilst others have reported significant differences in HRV between those with controlled and uncontrolled asthma (Lutfi, 2015) further work is warranted to elucidate the relationship between disease severity, duration, maturation and asthma with regards to the ANS response during exercise.

The present findings are partly in accord with the increased LF and TP reported following HIIT in adults (Heydari, et al., 2013; Kiviniemi, et al., 2014; Rakobowchuk, Harris, Taylor, Cubbon, & Birch, 2013), although the unchanged HF and decreased HFnu contradicts these studies. Furthermore, the current results disagree with the results from other HIIT studies in children (Gamelin, et al., 2009; Mandigout, et al., 2002). Specifically, Mandigout, et al. (2002) and Gamelin *et al*. (2009) reported no alterations in autonomic balance, despite significant increases in aerobic fitness. The discrepancies between these findings may be attributable to methodological differences, such as the duration and conditions under which the HRV measures were derived, the types of exercises and the duration of the intervention. Indeed, considerable differences in the duration of recordings used to obtain HRV, which ranged from three-minutes in the present study to 24-hours in

Mandigout *et al.* (2002), limit inter-study comparisons, particularly given that it is widely accepted to be inappropriate to compare parameters derived from different recording lengths (TaskForce, 1996). It is also important to highlight that whilst Mandigout *et al.* (2002) used high-intensity, intermittent exercises, they did not specifically implement a HIIT intervention. The longer duration of the intervention in the present study may also explain the significant influences on autonomic balance that were not reported in earlier studies in children (Gamelin, et al., 2009; Mandigout, et al., 2002). However, significant HRV adaptations can occur after two to three weeks in adults (Kiviniemi, et al., 2014; Seals & Chase, 1989). Whilst the applicability of these findings to younger populations remains to be elucidated, these findings suggest that training adaptations could have occurred in shorter interventions. Interestingly, the present results indicate that the influence of HIIT on ANS is age- or maturity-, dependant, with pre-pubertal children less sensitive and less able to induce training-related adaptations (Gilliam & Freedson, 1980; Katch, 1983). This potential influence of maturity may be particularly important when trying to understand the complex interactions underpinning HRV responses, which are simultaneously influenced by both neural and humoral effects (Binah, Weissman, Itskovitz-Eldor, & Rosen, 2013).

Interestingly, the present study found an increase in LF power with HIIT which persisted even when changes in TP were accounted for, reflecting an increased sympathovagal balance. Although the physiological underpinnings of the LF band still remain to be conclusively determined (TaskForce, 1996), these changes suggest an increased sympathetic tone following three-months of training which decreased towards baseline values at six-months. These deleterious initial changes in autonomic balance may be attributable to training load, which plays a key factor in eliciting autonomic adaptations

(Gamelin, et al., 2009); a high training load, to which participants are not accustomed, can lead to overload and an accumulation of fatigue. Such fatigue is associated with a shift in autonomic balance from parasympathetic- to sympathetic-predominance (Mourot et al., 2004; Schmitt, Regnard, & Millet, 2015). Therefore, the change in LF and associated variables indicates an initial fatigue-related autonomic shift towards sympathetic predominance which, following adaptation to the exercise load, returned to baseline values at six-months. Indeed, it could be postulated that a longer study duration may have demonstrated a continued decline in LF, resulting in a parasympathetic predominance as typically reported following HIIT in adults (Heydari, et al., 2013; Kiviniemi, et al., 2014) and aerobic training in adolescents (Hedelin, Wiklund, Bjerle, & Henriksson- Larsén, 2000).

The degree of training-induced adaptation may be related to an individual's genetics, and the pre-training level of HRV (Buchheit & Gindre, 2006). Specifically, pre-training SDNN is strongly correlated to the magnitude of improvements observed post-training and it has been recommended that training is conducted more frequently, or at a higher intensity, in those with poorer pre-training HRV (Buchheit & Gindre, 2006). Therefore, the present results may reflect a high baseline HRV, thereby limiting the potential for improvements to be elicited through HIIT. The lack of comparable data regarding HRV during exercise limits further conclusions, but the relatively poor aerobic fitness at baseline in the current participants, the significant influence of the intervention on their aerobic fitness, and the strong correlation reported between HRV and $\dot{V}O_{2peak}$ are relevant to note (Buchheit & Gindre, 2006).

The decreased normalised HF (HFnu) observed in the present study at three- and six-months may be a reflection of an increased LF component, decreasing the relative contribution of HF when corrected for changes in TP, or a decrease in parasympathetic activity. Although elevated parasympathetic activity is more commonly reported following training (Buchheit & Gindre, 2006; Carter, Banister, & Blaber, 2003), studies employing pharmacological autonomic blockades to assess the heart rate and HRV response have reported decreased vagal activity in trained athletes (Furlan et al., 1993; Katona, McLean, Dighton, & Guz, 1982). Nevertheless, the application of such studies to paediatric populations is highly speculative and caution is required when drawing any further conclusions.

The present study utilised multiple repeat constant-work-rate transitions at each time-point, thus improving reliability of measures and counteracting the day-to-day variation in HRV (Schroeder et al., 2004). Nonetheless, there are a number of limitations that should be noted. Firstly, the length of the ECG recordings was shorter than recommended (TaskForce, 1996) and the sample size may be deemed low, although it is still comparable to previous studies which found significant effects of HIIT on ANS function (Rakobowchuk, et al., 2013). It would also have aided in the interpretation of the present findings to have resting values for HRV. Furthermore, asthma was self-reported and relied on the participants' understanding of disease severity, which was potentially mild and may not have been severe enough to elicit autonomic alterations (Emin, et al., 2012). The study may also have been subject to selection bias as those with more severe asthma may have chosen not to participate due to fear of exacerbation or exercise induced asthma.

In conclusion, the present findings suggest that HRV is not deleteriously influenced by asthma in adolescents during relative intensity exercise and only spectral power was influenced by the six-month HIIT intervention, despite eliciting significant increases in aerobic fitness. Whilst highlighting the dissociation between aerobic fitness and HRV, these results indicate that HIIT may be associated with short-term, deleterious shifts in autonomic balance towards greater sympathetic predominance during exercise due to physiological overload and fatigue, which are ameliorated within six-months.

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612 **Table 1** Baseline participant characteristics

	Asthma	**Healthy**
n	31	32
Age (years)	13.5 ± 0.9	13.4 ± 0.9
Height (cm)	161.0 ± 10.0	157.9 ± 8.2
Mass (kg)	57.6 ± 14.6	50.7 ± 11.6
BMI ($kg \cdot m^{-2}$)	22.0 ± 3.9	20.0 ± 3.1
$\dot{V}O_{2peak}$ ($l \cdot min^{-1}$)	2.10 ± 0.49	2.04 ± 0.50
MVPA (mins)	60.3 ± 33.5	57.0 ± 18.2

613 Mean ± SD. *n*, sample size; BMI, body mass index; $\dot{V}O_{2peak}$, peak oxygen uptake; MVPA,
614 moderate-to-vigorous physical activity
615

616

Table 2 Sub-sample characteristics of those who met the minimum adherence criteria

	Intervention	**Control**
n	13	13
Age (years)	13.3 ± 0.9	13.6 ± 1.0
Height (cm)	160.7 ± 8.8	159.5 ± 8.8
Mass (kg)	52.3 ± 11.2	53.7 ± 12.8
BMI ($kg \cdot m^{-2}$)	20.1 ± 3.2	20.8 ± 3.7
$\dot{V}O_{2peak}$ ($l \cdot min^{-1}$)	2.00 ± 0.42	2.09 ± 0.47
$\dot{V}O_{2peak}$ ($ml \cdot kg^{-0.45} \cdot min^{-1}$)	332 ± 51	362 ± 52
MVPA (mins)	47.9 ± 14.3	58.5 ± 24.8
FEV_1 ($l \cdot min^{-1}$)	2.96 ± 0.79	2.86 ± 0.82
FEV_1 (%)	98 ± 15	91 ± 15

Mean ± SD. *n*, sample size; BMI, body mass index; $\dot{V}O_{2peak}$, peak oxygen uptake; MVPA, moderate-to-vigorous physical activity; FEV_1, forced expiratory volume in one second

Table 3 HRV during light-intensity exercise over six-months

	Intervention				
	Baseline	**Three-months**	**Six-months**	**Baseline**	**T**
SDNN (ms)	37.3 ± 6.0	42.0 ± 3.2*	44.3 ± 4.7	45.6 ± 6.3	
RMSSD (ms)	32.7 ± 7.8	35.5 ± 5.4	37.7 ± 6.5	40.2 ± 8.1	
LF (ms^2)	564.5 ± 181.5	735.1 ± 126.7	661.3 ± 104.7	725.8 ± 188.3	6
LFnu	64.1 ± 3.1	62.5 ± 3.3	61.2 ± 3.7	60.5 ± 3.2	
HF (ms^2)	459.7 ± 201.2	457.4 ± 105.8	608.6 ± 149.3	505.6 ± 208.8	4
HFnu	35.3 ± 3.2	37.2 ± 3.3	38.5 ± 3.7	39.3 ± 3.3	
HF_{Bf} (ms^2)	706 ± 305	707 ± 173	864 ± 234	751 ± 316	
HF_{Bf} nu	47 ± 4	47 ± 4	49 ± 4	51 ± 4	
TP (ms^2)	1648 ± 519	1761 ± 313	1889 ± 276	1767 ± 538	
TP_{Bf} (ms^2)	1887± 590	2012 ± 344	2149 ± 342	2070 ± 612	
LF:HF	2.22 ± 0.35	2.23 ± 0.32	2.12 ± 0.31	2.08 ± 0.36	
LF:HF_{Bf}	1.30 ± 0.18	1.38 ± 0.22	1.32 ± 0.19	1.23 ± 0.19	
SD1 (ms)	23.4 ± 5.5	25.2 ± 3.8	27.2 ± 4.6	28.5 ± 5.7	
SD2 (ms)	46.9 ± 6.8	53.4 ± 3.9*	55.7 ± 4.2*	55.23 ± 7.1	
SampEn	1.68 ± 0.07	1.63 ± 0.07	1.68 ± 0.08	1.61 ± 0.07	
DFAα1	1.07 ± 0.06	1.11 ± 0.07	1.04 ± 0.06	1.02 ± 0.07	
DFAα2	0.84 ± 0.05	0.86 ± 0.03	0.83 ± 0.04	0.79 ± 0.05	

Mean ± SD. SDNN, standard deviation of all the RR intervals; RMSSD, Root mean square of successive RR in
low frequency power (0.04-0.15 Hz); HF, high frequency power (0.15-0.4 Hz); HFnu, high frequency power in
, expanded high frequency power (0.15-*Bf* Hz); TP, total power; TP_{Bf}, total expanded power; LF:HF, low and hig
a ratio; LF:HF_{Bf}, low and expanded high frequency powers as a ratio; nu, normalized power; SD1 and SD2, Star
Poincaré Plot; SampEn; Sample entropy within the RR data; DFA, detrended fluctuation analysis of short-term (
HRV indices. * Significant difference to baseline within group *($p < 0.05$)*

Table 4 HRV during heavy-intensity exercise over six-months

	Intervention				
	Baseline	**Three-months**	**Six-months**	**Baseline**	**T**
SDNN (ms)	9.8 ± 0.9	9.3 ± 1.3	10.3 ± 4.3	10.4 ± 0.9	
RMSSD (ms)	10.6 ± 0.9	7.7 ± 1.3	9.7 ± 1.7	9.8 ± 1.5	
LF (ms^2)	6.0 ± 3.9	10.3 ± 1.9*	4.0 ± 0.6	10.9 ± 4.1	
LFnu	61.1 ± 5.2	72.0 ± 5.3*	68.6 ± 5.9	62.8 ± 5.4	
HF (ms^2)	3.8 ± 1.4	3.9 ± 1.2	2.3 ± 0.7	3.9 ± 1.4	
HFnu	37.7 ± 5.1	29.0 ± 5.1*	31.0 ± 0.7*	36.7 ± 5.3	
HF_{Bf} (ms^2)	23 ± 6	21 ± 5	20 ± 7	20 ± 6	
HF_{Bf} nu	75 ± 5	79 ± 11	72 ± 4	71 ± 5	
TP (ms^2)	26 ± 16	49 ± 9*	17 ± 3	43 ± 16	
TP_{Bf} (ms^2)	46 ± 17	65 ± 11	35 ± 7	60 ± 18	
LF:HF	2.60 ± 0.64	5.19 ± 0.83*	3.80 ± 0.59	3.98 ± 0.66	2
LF:HF_{Bf}	0.45 ± 0.15	0.75 ± 0.14*	0.46 ± 0.09	0.59 ± 0.15	0
SD1 (ms)	7.5 ± 1.0	5.4 ± 1.0	6.8 ± 1.2	7.1 ± 1.1	
SD2 (ms)	11.1 ± 1.1	10.2 ± 1.0	12.0 ± 1.0	12.4 ± 1.2	
SampEn	1.50 ± 0.09	1.59 ± 0.10	1.35 ± 0.11	1.50 ± 0.09	
DFAα1	0.43 ± 0.06	0.56 ± 0.05	0.42 ± 0.04	0.45 ± 0.06	
DFAα2	1.03 ± 0.07	1.07 ± 0.08	1.04 ± 0.09	1.03 ± 0.07	

Mean ± SD. SDNN, standard deviation of all the RR intervals; RMSSD, Root mean square of successive RR in
low frequency power (0.04-0.15 Hz); HF, high frequency power (0.15-0.4 Hz); HFnu, high frequency power in
, expanded high frequency power (0.15-*Bf* Hz); TP, total power; TP_{Bf}, total expanded power; LF:HF, low and hig
a ratio; LF:HF_{Bf}, low and expanded high frequency powers as a ratio; nu, normalized power; SD1 and SD2, Star
Poincaré Plot; SampEn; Sample entropy within the RR data; DFA, detrended fluctuation analysis of short-term (
HRV indices. * Significantly different to baseline within group *($p < 0.05$)*