1 **Asthma, body mass and aerobic fitness, the relationship in adolescents: the**

2 **eXercise for Asthma with Commando Joe's® (X4ACJ) trial**

3 **Running head: Relationship between asthma, body mass and fitness**

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33   **Abstract**

34   Although an association has been suggested between asthma, obesity, fitness and

35   physical activity, the relationship between these parameters remains to be elucidated

36   in adolescents.

37   Six-hundred and sixteen adolescents were recruited (334 boys; 13.0±1.1years;

38   1.57±0.10m; 52.6±12.9kg), of which 155 suffered from mild-to-moderate asthma (78

39   boys). Participants completed a 20-metre shuttle run test, lung function and 7-day

40   objective physical activity measurements and completed asthma control and quality

41   of life questionnaires. Furthermore, 69 adolescents (36 asthma; 21 boys) completed

42   an incremental ramp cycle ergometer test.

43   Although participants with asthma completed significantly fewer shuttle runs than

44   their peers, peak $\dot{V}O_2$ did not differ between the groups. However, adolescents with

45   asthma engaged in less physical activity (53.9±23.5 vs 60.5±23.6minutes) and had

46   higher BMI (22.2±4.8 vs 20.4±3.7kg·m^{-2}), than their peers. Whilst a significant

47   relationship was found between quality of life and cardiorespiratory fitness

48   according to peak $\dot{V}O_2$, only BMI was revealed as a significant predictor of asthma

49   status.

50   The current findings highlight the need to use accurate measures of cardiorespiratory

51   fitness rather than indirect estimates to assess the influence of asthma during

52   adolescence. Furthermore, the present study suggests that BMI and fitness may be

53   key targets for future interventions seeking to improve asthma quality of life.

54

57

Introduction

Asthma is one of the most common chronic childhood diseases (Wanrooij, Willeboordse, Dompeling, & van de Kant, 2014). The prevalence of asthma in the UK has dramatically risen over the last few decades, with 1 in 11 children currently diagnosed with the condition (Asthma UK, 2017). This increase in asthma prevalence has been accompanied by a concurrent increase in obesity (Townsend et al., 2013) and decrease in physical activity levels (Berntsen, 2011). Indeed, although the mechanisms and directionality remain unclear (McNarry, Boddy, & Stratton, 2014), recent studies have reported an association between asthma, obesity and fitness (Chen, Dong, Lin, & Lee, 2013; McNarry et al., 2014), with some studies even proposing a new phenotype of asthma related to a lack of cardiorespiratory fitness and/or physical activity. Indeed, as identified in Winn et al. (2017) adolescents with asthma fear asthma attacks and consequently withdraw from exercise which could be related, at least in part, to a reduced cardiorespiratory fitness and physical activity.

Despite the importance of physical activity and exercise as tools to ameliorate asthma symptoms, current evidence regarding the fitness levels of those with asthma is equivocal, with some studies finding those with asthma to have poorer fitness (McNarry et al., 2014; Villa et al., 2011), whilst others show no difference between those with asthma and their healthy peers (Berntsen et al., 2009; Pianosi & Davis, 2004; Santuz, Baraldi, Filippone, & Zacchello, 1997). These discrepancies may be due to asthma severity, with participants with more severe asthma having reduced fitness in comparison to their mild asthma or healthy peers. Furthermore the discrepancies may be related to the estimation of cardiorespiratory fitness from field-based measures which are subject to significant inaccuracies dependent on self-

83   motivation and peer influence (Cairney, Hay, Faught, Leger, & Mathers, 2008).

84   Moreover, even in studies which have utilised peak oxygen uptake ($\dot{V}O_2$) as a

85   measure of cardiorespiratory fitness, the applicability of this measure to functional

86   capacity during activities of daily living has been questioned (Jones, 2006). It is

87   especially important to account for body size during puberty around peak height

88   velocity due to increases in body mass potentially outweighing increases in peak

89    $\dot{V}O_2$. Indeed, the use of scaling peak $\dot{V}O_2$ is of particular importance in asthma

90   populations due to the distinct obese asthma phenotype suggested. Whilst some

91   studies have utilised ratio scaling (Berntsen, et al., 2009; van Veldhoven, et al.,

92   2001), in which issues such as biasing results when comparing children who vary

93   greatly in body mass have recently been highlighted (Loftin, Butz, Duggan, &

94   Serwint, 2016), no studies have used allometric scaling of peak $\dot{V}O_2$. Furthermore,

95   differences between those with and without asthma may be detected using other

96   parameters of aerobic fitness (Lucia, Hoyos, Perez, Santalla, & Chicharro, 2002). As

97   asthma affects the airways, this may cause derangements in the O_2 delivery,

98   subsequently increasing the mean response time to exercise ($\dot{V}O_2$ kinetics).

99   Moreover, if adolescents experience an increased O_2 delivery this may influence the

100   total O_2 cost of exercise ($\dot{V}O_2$ gain). However, despite the insight they potentially

101   provide, there is currently a lack of research considering the influence of asthma on

102   these submaximal parameters of cardiorespiratory fitness. Furthermore, whilst

103   insufficient physical activity has been associated with the development of asthma

104   (Sherriff, et al., 2009), physical activity has largely been assessed through self-report

105   questionnaires, which are poorly correlated with objective measures (Tsai, Ward,

106   Lentz, & Kieckhefer, 2012).

107   There is a strong positive correlation between cardiorespiratory fitness and physical

108   activity among adolescents with asthma (Berntsen, et al., 2013; Vahlkvist, Inman, &

109   Pedersen 2010). Moreover, there is a strong negative relationship between physical

110   activity and obesity (Walders-Abramson, et al. 2009). Each of these factors have

111   previously been shown to be related to asthma occurrence, but no study to date has

112   attempted to elucidate the relationships between asthma, fitness, physical activity

113   and obesity.

114   Therefore, the aim of the present study was to investigate the influence of asthma on

115   the submaximal and maximal parameters of cardiorespiratory fitness in adolescents.

116   Furthermore, this study sought to further elucidate the potential relationship between

117   cardiorespiratory fitness, physical activity, body mass and asthma.

118

Methods

Participants

Six-hundred and sixteen adolescents (334 boys; 96% white; Table 1), of which 155 suffered from asthma (78 boys), from five schools across South Wales agreed to participate in the study as part of a wider randomised control trial (the X4A trial: eXercise for Asthma with Commando Joe's®). The total population eligible to participate in the study was approximately 1,900, representing a study uptake of 32%. Ethical approval was granted by the institutional research ethics committee (ref: 140515 and PG/2014/29). Parent/guardian and head teacher consent and child assent were obtained prior to participation.

Procedures

Anthropometrics

Body mass and stature were measured according to the techniques outlined by International Society for the Advancement of Kinanthropometry (Stewart, Marfell-Jones, Olds, & de Ridder, 2011). Stature, sitting stature and waist circumference were measured to the nearest 0.01 m (Seca213, Hamburg, Germany) and body mass to the nearest 0.1 kg (Seca876, Hamburg, Germany). Body mass index (BMI) was subsequently calculated, along with BMI z-scores, and grouped using age and sex specific child percentiles as outlined by the Centres of Disease Control and Prevention (CDC) growth charts (Kuczmarski, et al., 2000) and presented as in previous research (Barlow, 2007). Further, lower limb length was calculated as the difference between stature and sitting stature and then used to determine maturity offset using the equations of Mirwald et al. (2002).

142 *Physical activity*

143 Physical activity levels were measured at 100 Hz using ActiGraph GT3X+

144 accelerometers (Actigraph, Pensacola, FL, USA) worn on the right hip for seven

145 consecutive days. Participants were instructed only to remove the monitor it if they

146 undertook water-based or contact activities, where required. The data were analysed

147 using KineSoft version 3.3.67 (KineSoft, Saskatchewan, Canada) employing 1

148 second epochs with sustained periods of at least 20-minutes of consecutive zeros

149 considered non-wear time (Catellier et al., 2005). A minimum daily wear time of 10

150 hours per day for 2 weekdays and 1 weekend day was used (Rich et al., 2013).

151 Physical activity intensities were calculated using Evenson et al. (2008) cut points,

152 which have been shown to be valid and reliable determinats of activity intensity in

153 children and adolescents (Trost, Loprinzi, Moore, & Pfeiffer, 2011).

154 *Lung function*

155 Forced Expiratory Volume in 1 second (FEV_1), Forced Vital Capacity (FVC),

156 FEV_1/FVC ratio, Peak Expiratory Flow (PEF), and Forced Expiratory Flow between

157 25-75% of vital capacity (FEF_{25-75}) was measured using a portable dry spirometer

158 (Vitalograph, Buckingham, UK). The best of three measurements were taken

159 according to American Thoracic Society guidelines (1995) and to the standardised

160 protocol (Miller, et al., 2005) and expressed as a percentage of the age-sex-stature

161 predicted values dependant on ethnicity (Hankinson, Odencrantz, & Fedan, 1999;

162 Quanjer, et al., 1993; Rosenthal, et al., 1993).

163 *Fractional Exhaled Nitric Oxide*

164 Participants with asthma were asked to perform a Fraction Exhaled Nitric Oxide

165 (FeNO) test, a marker of airway inflammation in asthma, prior to spirometric testing.

166 The FeNO test was performed in a seated position and in accordance with the

167 American Thoracic Society guidelines (Dweik et al., 2011). Participants were asked

168 to exhale away from the device (NIOX MINO, Aerocrine AB, Solna, Sweden) and

169 then inhale to total lung capacity through the device before immediately exhaling for

170 10 seconds at 50 ± 5 ml·sec^{-1}. Visual and audio cues were provided by the computer

171 software throughout. One test was completed and the final three seconds of

172 exhalation were evaluated.

173 *Asthma control*

174 Asthma control was measured using the Asthma Control Questionnaire (ACQ)

175 (Juniper, Gruffydd-Jones, Ward, & Svensson, 2010) which consists of 7-items

176 relating to recent symptoms, medications and FEV$_1$ score. Each item of the ACQ

177 was scored from 0 to 6 and then averaged to give an overall result. Scores of ≤0.75

178 or ≥1.5 indicated well-controlled and poorly-controlled asthma, respectively. Internal

179 consistency, measured using Cronbach's alpha coefficients (Cronbach, 1951), for the

180 ACQ were deemed acceptable ($\alpha = 0.77$).

181 *Asthma-related quality of life*

182 The Paediatric Asthma Quality of Life Questionnaire (PAQLQ) was used to assess

183 the symptoms, activity limitations and emotional and environmental effects of

184 asthma (Juniper et al., 1996). The PAQLQ consists of 23 questions (scored on a

185 Likert scale from 1 to 7), with a higher score indicating a better asthma status.

186 Internal reliability for the PAQLQ was deemed excellent ($\alpha = 0.97$).

Quality of life

The Pediatric Quality of Life Inventory (PedsQL) Teenager Report (Version 4.0) (Varni, Seid, & Rode, 1999) was used to compare the perceived quality of life between those participants with and without asthma. A widely validated measure in adolescents (Varni, Burwinkle, & Seid, 2006; Varni, Burwinkle, Seid, & Skarr, 2003), the, the PedsQL consists of 23 items focusing on participants' physical, emotional, social and school functioning quality, with a higher score indicative of a better quality of life. Internal reliability for the PedsQL was excellent ($\alpha = 0.90$).

Asthma severity

Asthma severity was classified as mild, moderate or severe according to the Global Initiative for Asthma guidelines (Global Initiative for Asthma, 2017), using the medication step required to achieve asthma control. Medication step was assessed by questionnaire to establish what medication participants with asthma were prescribed and how frequently it was administered. Severity classification was agreed with a Respiratory Physician (GAD). For the purpose of analysis, moderate and severe asthma were grouped to power the statistics. Participants were excluded if they did not have stable asthma (n = 4).

Cardiorespiratory fitness

Participants were asked to refrain from strenuous exercise and avoid consuming food for 24h and 2h prior to the exercise test, respectively.

   20-metre shuttle run

Cardiorespiratory fitness was estimated using the 20-metre progressive shuttle run test, a previously validated field measure in children (Mayorga-Vega, Aguilar-Soto,

210 & Viciana, 2015). The number of shuttles completed before voluntary exhaustion

211 were recorded.

212   Peak $\dot{V}O_2$

213 Sixty-nine adolescents (39 boys) inclusive of 36 with asthma (21 boys) were

214 selected, using stratified randomisation, to complete incremental ramp tests. The

215 groups were stratified by age, sex and asthma to provide a representative sample of

216 the wider population. Participants performed an incremental ramp exercise test to

217 volitional exhaustion, defined as a drop in cadence >10 rpm for five consecutive

218 seconds, on an electromagnetically braked cycle ergometer (Ergoselect 200, Ergoline

219 GmbH, Lindenstrasse, Germany). The ramp protocol consisted of 3 minutes of

220 "unloaded" pedalling (0 W) followed by an increase in work rate of 12-24 W·min^{-1}

221 dependent on pre-baseline familiarisation incremental ramp tests. Throughout the

222 test, participants were asked to keep the cadence at 75 ± 5 revolutions per minute.

223 Pulmonary ventilation (VE) and gas exchange ($\dot{V}O_2$ and $\dot{V}CO_2$) were measured

224 breath by breath (Jaeger Oxycon Mobile, Jaeger, Hoechberg, Germany).

225 *Data analysis*

226 The peak $\dot{V}O_2$ was taken as the highest 10-second average value attained prior to the

227 end of the test, with the Gas Exchange Threshold (GET) determined using the V-

228 slope method (Beaver, Wasserman, & Whipp, 1986). The interpretation of studies

229 investigating peak $\dot{V}O_2$ is often hindered by not accounting for a possible influence

230 of body size, especially in youth and populations in associated with significant

231 differences in body mass/size. This study includes absolute, ratio-scaled and

232 allometrically scaled peak $\dot{V}O_2$ for comparison with previous studies and to examine

233 differences between each of the methods of reporting peak $\dot{V}O_2$. Specifically,

analysis of covariance (ANCOVA) was used to allometrically account for the influence of body size using log transformed data. Common allometric exponents were confirmed for the data and power function ratios (Y/X^b) were computed.

Baseline $\dot{V}O_2$ was taken as the average of the first 45 seconds of the last minute prior to the increase in work rate. Breath-by-breath data were then averaged into 10-second time bins and the gain and mean response time (MRT) calculated according to the methods reported by Barstow et al. (2000). Specifically, the gain ($\Delta \dot{V}O_2$ / ΔW) was determined by linear regression over three segments: S_1 gain, is the gain from 1-minute into the ramp test up to GET; S_2 gain, is the gain from GET to peak $\dot{V}O_2$; and S_T, is the gain over the range of $S_1 + S_2$. The MRT was calculated as the point of intersection between the baseline $\dot{V}O_2$ and a backwards linear extrapolation of the $\dot{V}O_2$ by time slope from the onset of the increase in work rate (Glantz 1990). The MRT was also determined using two segments, S_1 (MRT_1) and S_T (MRT_T) (Whipp, Davis, Torres, & Wasserman, 1981).

Statistical analysis

Shapiro-Wilk tests were used to examine the normality of the data prior to any analyses. In the case of normally distributed data, independent sample t-tests were used to assess differences between participants with and without asthma. A Mann-Whitney U test was used when data were not normally distributed. Analysis of covariance was used to investigate the influence of asthma on cardiorespiratory fitness and its interaction with sex, age and maturity. One-way ANOVA tests were also used to determine the influence of the level of asthma severity. Pearson's correlation coefficients were used to investigate the degree of association between key variables. Furthermore, the association between asthma and BMI was assessed

258   by logistic regression adjusting for fitness and time spent in moderate-to-vigorous

259   physical activity (MVPA). Missing data were imputed using multiple imputation for

260   physical activity data, this was done using all other measures for each participant to

261   predict the missing value. All statistical analyses were conducted using SPSS v22

262   (IBM Corp, Armonk, NY). All data are presented as mean ± standard deviation (SD)

263   where parametric and medians and ranges for non-parametric data with statistical

264   significance accepted as $P < 0.05$.

265

Results

Those with asthma were predominantly characterised as having mild, persistent asthma (85%), with the minority having moderate or severe asthma (15%) (Global Initiative for Asthma, 2017). There were no significant differences between participants with mild and moderate or severe asthma and therefore all results are presented as differences between asthma and non-asthma participants. As shown in Table 1, no anthropometric differences were shown between those with and without asthma, with the exception of body mass and waist circumference which were significantly higher in those with asthma. Similarly, those with asthma had a significantly ($P < 0.01$) higher BMI (22.2 ± 4.8 kg·m^{-2}) than their healthy peers (20.4 ± 3.7 kg·m^{-2}). Age-specific BMI percentiles revealed 41.9% of participants with asthma were overweight or obese, in comparison to 25.4% of healthy participants. However, the BMI z-scores placed the mean of the participants both with and without asthma within the "healthy" range. Participants with asthma spent significantly ($P < 0.05$) less time in both moderate (31.1 ± 11.7 minutes) and vigorous (22.9 ± 13.2 minutes) physical activity per day than their healthy peers (34.6 ± 13.1 and 25.9 ± 13.2, respectively). A lower FEV$_1$% and more marked small airways obstruction (FEF$_{25-75}$%) was observed in those with asthma. However, those with asthma did not have an obstructed FEV$_1$/FVC ratio, consistent with most having mild asthma.

As shown in Table 2, the ACQ revealed 32% of participants had well-controlled asthma (score <0.75), 36% had intermediate control and the remaining 32% had poorly controlled asthma (score >1.5). According to the PAQLQ, 14% of participants with asthma reported a score less than 4, with 5% scoring 7. Although

290 the mean of the PAQLQ is relatively high, 95% scored less than 7 indicating at least

291 some degree of impairment.

292 In contrast to the 20-metre shuttle run in which healthy participants completed

293 significantly more shuttles than those with asthma (48 ± 24 vs 42 ± 23 shuttles,

294 respectively), peak $\dot{V}O_2$ and scaled peak $\dot{V}O2$ did not differ according to asthma

295 status (Table 3). Similarly, there were no significant differences between asthma and

296 non-asthma groups in the absolute or relative GET or the gain. However, participants

297 with asthma did have a significantly shorter MRT_T, although these differences were

298 not observed below the GET and were ameliorated once work rate was added as a

299 covariate.

300 Although significant differences were shown between girls and boys for

301 cardiorespiratory fitness and physical activity levels, sex did not account for any of

302 the variance between asthma and non-asthma groups. Therefore, boys and girls were

303 pooled for all subsequent analyses. The number of shuttles completed in the 20-

304 metre shuttle run was negatively correlated with BMI ($r = -0.34$, $P < 0.05$) and

305 positively associated with MVPA ($r = 0.34$, $P < 0.05$) pooled for both those with and

306 without asthma. Body mass index was also negatively associated with MVPA ($r = -$

307 0.18, $P < 0.05$). Positive associations were shown between cardiorespiratory fitness

308 according to both the 20-metre shuttle run and peak $\dot{V}O_2$ and ACQ ($r = -0.15$ and $-$

309 0.35; $P < 0.05$), PAQLQ ($r = 0.27$ and 0.34, $P < 0.05$) and PedsQL ($r = 0.22$ and

310 0.35, $P < 0.05$). Furthermore, participants without asthma reported a significantly

311 higher quality of life ($78.2 ± 14.7$ vs $74.4 ± 17.8$). Whilst significant, these

312 correlations are weak and should be interpreted with caution.

313   As BMI, 20-metre shuttle run and MVPA were significantly different between the

314   asthma and non-asthma groups, univariate logistic regression analyses were

315   performed on each. Both BMI and fitness were shown to be significantly associated

316   with asthma; MVPA failed to reach significance (P = 0.06) even when using

317   multiple imputation to replace missing MVPA data. Multivariate logistic regression

318   (Table 4) revealed BMI as an independent factor associated with asthma.

319

Discussion

The present study highlights the importance of the measure of cardiorespiratory fitness used when investigating the influence of asthma in adolescents. Specifically, contrary to the findings reported here and elsewhere with regards to the 20-metre shuttle run, when more accurate and sensitive measures of cardiorespiratory fitness are used, there was no difference between those with and without asthma. Furthermore, the present study reveals obesity to be a significant predictor of asthma status and those with asthma to engage in less MVPA. Taken together, these findings highlight important potential targets for future interventions that seek to reduce asthma severity and prevalence.

The current participants with asthma reported a lower quality of life than their healthy counterparts, in agreement with previous studies (Merikallio, Mustalahti, Remes, Valovirta, & Kaila, 2005; Molzon et al., 2013), although it is pertinent to note that the majority were characterised by poor asthma control which is likely to have reduced their quality of life over and above the effects of asthma *per se* (Sundbom, Malinovschi, Lindberg, Alving, & Janson, 2016). Interestingly, only fitness was shown to be related to quality of life and asthma control, although this was a weak correlation, fitness could possibly represent a key target to improve quality of life in those with asthma as observed in previous studies (Andersen et al., 2017; Fanelli, Cabral, Neder, Martins, & Carvalho, 2007). Such improvements in fitness may be elicited through improvements in BMI and physical activity which were associated with fitness in the current study. Indeed, whilst the mean BMI z-score of both those with and without asthma revealed the participants had a "healthy" BMI, those with asthma not only demonstrated a higher BMI, in accord with previous studies (Black, Smith, Porter, Jacobsen, & Koebnick, 2012; McNarry

et al., 2014), but also a significantly lower MVPA (Sousa, Cabral, Martins, & Carvalho, 2014; Villa et al., 2011), with the majority of those with asthma failing to meet the recommended guidelines of 60-minutes MVPA per day (Department of Health, 2011). These low MVPA levels may be attributable to a fear of asthma attack associated with exercise. Indeed, exercise-induced bronchoconstriction (EIB) is common in adolescents with asthma and the occurrence of symptoms has been found to discourage physical activity, especially in those with more severe asthma (Lang et al., 2004). However, contrastingly, exercise-related activities were still cited as the most enjoyable activity by over 80% of adolescents with asthma (Winn et al., 2017).

The current cardiorespiratory fitness results significantly differed according to their method of determination. Specifically, according to the 20-metre shuttle run, those with asthma were significantly less fit than their healthy counterparts but both groups demonstrated a relatively high degree of fitness relative to recently generated receiver operating characteristic cut-points (Boddy et al., 2012). In contrast, using the gold standard measure of cardiorespiratory fitness of peak $\dot{V}O_2$ (Carey & Richardson, 2003), those with asthma were comparable to those without asthma. These results were also comparable to previous research, although slightly lower which is likely attributable to the use of a cycle ergometer rather than treadmill (37 - 41 $ml \cdot min^{-1} \cdot kg^{-1}$ vs. 35 - 48 $ml \cdot min^{-1} \cdot kg^{-1}$) (Armstrong, 2006). This discrepancy could be due to self-perceptions and peer-perceptions of (in)ability (Winn et al., 2017), causing those with asthma to limit their performance in front of others compared to when tested in isolation or on a non-familiar modality (Glazebrook et al., 2006). It could also be suggested that such perceptions may be exacerbated by the greater BMI of those with asthma, as it is frequently cited that those who are overweight are unwilling to exercise in front of their peers (Ball, Crawford, & Owen,

370   2000). Furthermore, the discrepancies in the 20-metre shuttle run between

371   participants with and without asthma may have been due to EIB limiting some

372   participants with asthma, possibly resulting in the early dropout from the measure.

373   The lack of effect of asthma on peak $\dot{V}O_2$ in the present study agrees with previous

374   studies (Berntsen et al., 2009; Pianosi & Davis, 2004; Santuz et al., 1997) and

375   suggests that previous studies utilising indirect estimates of cardiorespiratory fitness

376   may have drawn erroneous conclusions (Cairney et al., 2008; McNarry et al., 2014),

377   as would also have been done according to the current 20-metre shuttle run results.

378   The relatively low peak $\dot{V}O_2$ values (Rodrigues, Perez, Carletti, Bissoli, & Abreu,

379   2006) reported in this study nonetheless highlight an area of concern with regards to

380   the current health of adolescents (Ortega, Ruiz, Castillo, & Sjostrom, 2008). Indeed,

381   considering that peak $\dot{V}O_2$ is one of the strongest predictors of all-cause mortality

382   (Kodama et al., 2009), with a strong relationship between peak $\dot{V}O_2$ as a child and

383   adult (Malina, 2001), the current results highlight the need for interventions that

384   successfully, and sustainably, increase the cardiorespiratory fitness of youth.

385   This is the first study to consider the influence of asthma on the sub-maximal

386   parameters of aerobic fitness (MRT, gain and GET), many of which have been

387   suggested to be more sensitive to both advantageous and deleterious adaptations than

388   peak $\dot{V}O_2$ (McNarry, Harrison, Withers, Chinnappa, & Lewis, 2017). However, in

389   agreement with peak $\dot{V}O_2$, no influence of asthma was manifest on any parameter of

390   aerobic fitness. Whilst other respiratory diseases have been found to be associated

391   with significant differences in gain between those with and without the condition

392   (Fielding et al., 2015), participants with asthma were not different to their peers.

393   These findings suggest that adolescents with asthma do not engender a greater O_2

394   cost of exercise in comparison to their peers. The findings on the GET suggest that

395 those with asthma are able to participate in similar training programmes as those

396 without. Although optimal training should be based on an individuals' GET, as

397 differences were not shown, those with asthma will have comparable training

398 "zones" that should elicit similar improvements. These findings are in accord with

399 previous research showing no differences between asthma and their healthy

400 counterparts (Santuz et al., 1997). Whilst the GET was low in comparison to

401 previous findings (Fawkner and Armstrong 2004), the results do not suggest

402 deconditioning (<50% peak $\dot{V}O_2$) (Urquhart & Vendrusculo, 2017). In contrast, it is

403 perhaps interesting to note the significantly longer MRT found here than in

404 previously reported research (Barstow, Jones, Nguyen, & Casaburi, 2000; McNarry,

405 Welsman, & Jones, 2011), which may suggest chronic deconditioning and agreeing

406 with the relatively low peak $\dot{V}O_2$ values observed from the cycle ergometer. These

407 findings must be interpreted with caution however due to the influence of ramp rate

408 on the MRT which limits inter-study comparisons (Boone, Koppo, & Bouckaert,

409 2008). The lack of a difference between adolescents with and without asthma in peak

410 $\dot{V}O_2$ and subsequently the MRT suggests that any derangements in airways of the

411 participants with asthma do not affect the O_2 delivery to the mitochondria within the

412 muscle.

413 In agreement with previous studies (McNarry et al., 2014; Vahlkvist, Inman, &

414 Pedersen, 2010), the prevalence of overweight and obesity in the present participants

415 with asthma was high in comparison to their peers. Whilst the causal relationship

416 between asthma and obesity remains unclear, postulated mechanisms include co-

417 morbidities or mechanical effects of an increased pressure caused by excess tissue

418 mass in the abdomen and chest influencing hyper-responsiveness or symptoms of

419 asthma directly (Farah & Salome, 2012). Alternatively, or additionally, the increased

BMI in those with asthma could be related to the over-diagnosis of asthma in obese people (van Huisstede et al., 2013), with obesity significantly influencing many spirometric parameters (Spathopoulos et al., 2009).

There was a large range of FeNO score with the mean (42.7 ± 44.0ppb) considered high (children >35ppb, adults >50ppb) (Dweik et al., 2011). The current FeNO scores were also higher than reported elsewhere in well-controlled asthma (Willeboordse, van de Kant, van der Velden, van Schayck, & Dompeling, 2016), indicating sub-optimal control of airway inflammation and raising the possibility of poor inhaler technique and/or poor medication adherence. This is a significant problem, especially in youth with asthma who cite barriers to physical activity such as administering medication in front of their peers and embarrassment of their condition (Cohen, Franco, Motlow, Reznik, & Ozuah, 2003). When reporting their medication and adherence, participants often described taking their prescribed preventer sporadically and not as directed (Chapman et al., 2017). This poor control is likely to exacerbate EIB, further reinforcing their perception of an inability to, and fear of, exercise. Therefore, a potential solution to their lack of fitness and physical activity and increased BMI could be as simple as education on proper inhaler technique.

A major strength of this study was the use of more sensitive parameters of aerobic fitness (GET, MRT and gain) which have not been previously assessed in adolescents with asthma. However, it is pertinent to note, a "verification phase" or supramaximal test was not utilised following the peak $\dot{V}O_2$ measure. Furthermore the use of objective measures of physical activity should also be considered a strength of the study. The high proportion of participants with asthma relative to the national prevalence is likely due to the active encouragement of those that self-reported

445 having asthma to participate in the study. The lack of difference between participants

446 with mild and moderate or severe asthma may be due to the study not being powered

447 for subgroup analysis by severity. In addition, there may have been a self-selection

448 bias such that participants with more severe asthma and/or poorer fitness may have

449 chosen to opt out of more vigorous subsample testing (n = 3). Finally, the different

450 modalities of the field and lab-based measures of cardiorespiratory fitness limits our

451 interpretation to some extent. Whilst a treadmill may have been more comparable to

452 the 20-metre shuttle run test, the cycle ergometer was used for the pragmatic reasons,

453 participant familiarity and to reduce movement artefact for other measures not

454 associated with this manuscript.

455 **Conclusion**

456 In conclusion, adolescents with predominantly mild persistent asthma do not differ

457 in cardiorespiratory fitness from their peers, however, they do have an increased

458 BMI and engage in less MVPA. The present findings also highlight the importance

459 of using appropriate measures of cardiorespiratory fitness to determine the influence

460 of disease on exercise responses. Finally, although only a weak relationship was

461 found between cardiorespiratory fitness and quality of life, further studies should

462 investigate if cardiorespiratory fitness can reduce asthma severity in adolescents with

463 more severe asthma.

464

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708 **Table 1. Anthropometric measures for participants with and without**
709 **asthma**

	n (Asthma / Non-asthma)	Asthma	Non-asthma	P-value
Age (years)	155 / 457	13.0 ± 1.1	13.0 ± 1.1	0.45
Stature (cm)	137 / 415	156.5 ± 9.9	157.4 ± 9.7	0.38
Body mass (kg)	136 / 415	54.5 ± 14.8	51.0 ± 12.4	0.01*
Sitting stature (cm)	137 / 415	78.6 ± 5.2	79.3 ± 5.3	0.11
Waist circumference (cm)	135 / 414	73.7 ± 12.2	68.5 ± 9.7	< 0.01*
Age from PHV (years)	136 / 415	-0.2 ± 1.3	-0.3 ± 1.4	0.58
BMI (kg·m^{-2})	136 / 415	22.2 ± 4.8	20.4 ± 3.7	< 0.01*
BMI z-score	136 / 415	0.71 ± 1.05	0.33 ± 0.99	< 0.01*

710   * = Significant P<0.05; PHV = Peak height velocity; BMI = Body mass index

711 **Table 2. Characteristics of participants with and without asthma**

	n (Asthma / Non-asthma)	Asthma	Non-asthma	P-value
20-metre shuttle run (shuttles)	138 / 395	36.5 (10-120)	43.0 (8-127)	0.01*
MPA (min)	61 / 177	29.5 (13.1-65.4)	32.8 (7.0-83.3)	0.03*
VPA (min)	61 / 177	20.1 (5.4-83.2)	23.7 (3.1-95.9)	0.04*
MVPA (min)	61 / 177	49.4 (18.5-148.6)	58.9 (12.6-153.3)	0.02*
FEV$_1$ (%Predicted)	143 / 411	91.0 ± 14.7	95.7 ± 16.4	< 0.01*
FVC (%Predicted)	143 / 411	99.0 ± 14.2	99.7 ± 14.1	0.57
FEF$_{25-75}$ (%Predicted)	143 / 411	76.0 ± 25.3	87.0 ± 24.5	< 0.01*
PEF (%Predicted)	143 / 411	91.2 ± 19.6	89.8 ± 20.2	0.47
FEV$_1$/FVC	143 / 411	0.82 (0.58-0.99)	0.84 (0.58-0.99)	< 0.01*
FeNO (ppb)	139 / 0	42.7 ± 44.0	NA	NA
PedsQL PhH	132 / 400	81.3 (12.5-100)	84.4 (12.5-100)	0.10
PedsQL PsH	132 / 400	75.0 (20-100)	81.3 (13.3-100)	0.06
PedsQL Total	132 / 400	77.7 (19.6-100)	80.8 (13.0-100)	0.04*
ACQ	143 / 0	1.3 ± 1.0	NA	NA
PAQLQ Symptoms	143 / 0	5.5 ± 1.2	NA	NA
PAQLQ Activities	143 / 0	5.5 ± 1.2	NA	NA
PAQLQ Emotions	143 / 0	5.9 ± 1.3	NA	NA
PAQLQ	143 / 0	5.6 ± 1.2	NA	NA

712   Mean±SD or median (range); * = Significant p<0.05; NA = Not applicable;
713   MPA = moderate physical activity; VPA = Vigorous physical activity; MVPA
714   = Moderate-to-vigorous physical activity; %Predicted = Expressed as a
715   percentage of the age-sex-stature predicted value; FEV$_1$ = Forced Expiratory

716 Volume in 1 second; FVC = Forced Vital Capacity; FEF_{25-75} = Forced
717 Expiratory Flow between 25-75% of vital capacity; PEF = Peak Expiratory
718 Flow; FeNO = Fractional exhaled nitric oxide; PedsQL = Pediatric Quality of
719 Life Inventory; PhH = Physical score; PsH = Psychological score; ACQ =
720 Asthma control questionnaire; PAQLA = Paediatric Asthma Quality of Life
721 Questionnaire

722 **Table 3. Incremental ramp test results for participants with and**
723 **without asthma**

	Asthma	Non-asthma	P-value
Baseline $\dot{V}O_2$ (l·min^{-1})	0.60 ± 0.10	0.60 ± 0.10	0.70
$\dot{V}O_2$ peak (l·min^{-1})	2.00 ± 0.50	2.10 ± 0.50	0.67
$\dot{V}O_2$ BM (ml·kg^{-1}·min^{-1})	36.9 ± 8.3	41.1 ± 7.4	0.02*
$\dot{V}O_2$ Scaled (ml·kg$^{-0.57}$·min^{-1})	205.1 ± 43.6	221.6 ± 38.6	0.11
GET (l·min^{-1})	1.10 ± 0.30	1.00 ± 0.30	0.62
GET (%$\dot{V}O_2$)	53.8 ± 7.9	50.5 ± 6.2	0.06
MRT_T (s)	72.5 ± 17.5	81.5 ± 17.7	0.04*
MRT_1 (s)	69.6 ± 13.6	75.5 ± 17.0	0.12
S_1 Gain (ml·min^{-1}·W^{-1})	9.0 ± 1.8	9.1 ± 2.8	0.78
S_2 Gain (ml·min^{-1}·W^{-1})	10.8 ± 2.0	11.0 ± 1.3	0.55
S_T Gain (ml·min^{-1}·W^{-1})	10.0 ± 1.5	10.3 ± 1.4	0.49

724 Mean±SD; * = Significant $p<0.05$; NA = Not applicable; $\dot{V}O2$ = Oxygen
725 uptake; BM = body mass; GET = Gas exchange threshold; S_1 gain = Gain from
726 1-minute into ramp to GET; S_2 gain = Gain from GET to peak $\dot{V}O2$; S_T gain =
727 Gain over the total range S1 + S2; MRT_1 = Mean response time for S_1; MRT_T =
728 Mean response time for $S_1 + S_2$

729 **Table 4. Logistic regression analysis to test potential association with**
730 **asthma from Body Mass Index, Moderate-to-Vigorous Physical**
731 **Activity and 20-metre shuttle run**

	β (SE)	Wald	P-value	OR
Constant	2.24 (0.72)	9.97	< 0.01	9.41
BMI	-0.09 (0.02)	12.89	< 0.01	0.92
MVPA	0.01 (0.01)	1.09	0.28	1.01
Shuttle Run	0.01 (0.00)	2.18	0.19	1.01

732 β = coefficient; SE = standard error; OR = odds ratio; BMI = Body mass index;
733 MVPA = Moderate-to-vigorous physical activity
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