Asthma, body mass and aerobic fitness, the relationship in adolescents: the eXercise for Asthma with Commando Joe's® (X4ACJ) trial

Running head: Relationship between asthma, body mass and fitness

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Abstract

Although an association has been suggested between asthma, obesity, fitness and physical activity, the relationship between these parameters remains to be elucidated in adolescents.

Six-hundred and sixteen adolescents were recruited (334 boys; 13.0±1.1years; 1.57±0.10m; 52.6±12.9kg), of which 155 suffered from mild-to-moderate asthma (78 boys). Participants completed a 20-metre shuttle run test, lung function and 7-day objective physical activity measurements and completed asthma control and quality of life questionnaires. Furthermore, 69 adolescents (36 asthma; 21 boys) completed an incremental ramp cycle ergometer test.

Although participants with asthma completed significantly fewer shuttle runs than their peers, peak $\dot{V}O_2$ did not differ between the groups. However, adolescents with asthma engaged in less physical activity (53.9±23.5 vs 60.5±23.6minutes) and had higher BMI (22.2±4.8 vs 20.4±3.7kg·m^{-2}), than their peers. Whilst a significant relationship was found between quality of life and cardiorespiratory fitness according to peak $\dot{V}O_2$, only BMI was revealed as a significant predictor of asthma status.

The current findings highlight the need to use accurate measures of cardiorespiratory fitness rather than indirect estimates to assess the influence of asthma during adolescence. Furthermore, the present study suggests that BMI and fitness may be key targets for future interventions seeking to improve asthma quality of life.

Keywords: Obesity, quality of life, lung function, physical activity, cardiorespiratory fitness

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 selfmotivation and peer influence (Cairney, Hay, Faught, Leger, & Mathers, 2008). Moreover, even in studies which have utilised peak oxygen uptake ($\dot{V}O_2$) as a measure of cardiorespiratory fitness, the applicability of this measure to functional capacity during activities of daily living has been questioned (Jones, 2006). It is especially important to account for body size during puberty around peak height velocity due to increases in body mass potentially outweighing increases in peak $\dot{V}O_2$. Indeed, the use of scaling peak $\dot{V}O_2$ is of particular importance in asthma populations due to the distinct obese asthma phenotype suggested. Whilst some studies have utilised ratio scaling (Berntsen, et al., 2009; van Veldhoven, et al., 2001), in which issues such as biasing results when comparing children who vary greatly in body mass have recently been highlighted (Loftin, Butz, Duggan, & Serwint, 2016), no studies have used allometric scaling of peak $\dot{V}O_2$. Furthermore, differences between those with and without asthma may be detected using other parameters of aerobic fitness (Lucia, Hoyos, Perez, Santalla, & Chicharro, 2002). As asthma affects the airways, this may cause derangements in the O_2 delivery, subsequently increasing the mean response time to exercise ($\dot{V}O_2$ kinetics). Moreover, if adolescents experience an increased O_2 delivery this may influence the total O_2 cost of exercise ($\dot{V}O_2$ gain). However, despite the insight they potentially provide, there is currently a lack of research considering the influence of asthma on these submaximal parameters of cardiorespiratory fitness. Furthermore, whilst insufficient physical activity has been associated with the development of asthma (Sherriff, et al., 2009), physical activity has largely been assessed through self-report questionnaires, which are poorly correlated with objective measures (Tsai, Ward, Lentz, & Kieckhefer, 2012).

There is a strong positive correlation between cardiorespiratory fitness and physical activity among adolescents with asthma (Berntsen, et al., 2013; Vahlkvist, Inman, & Pedersen 2010). Moreover, there is a strong negative relationship between physical activity and obesity (Walders-Abramson, et al. 2009). Each of these factors have previously been shown to be related to asthma occurrence, but no study to date has attempted to elucidate the relationships between asthma, fitness, physical activity and obesity.

Therefore, the aim of the present study was to investigate the influence of asthma on the submaximal and maximal parameters of cardiorespiratory fitness in adolescents. Furthermore, this study sought to further elucidate the potential relationship between cardiorespiratory fitness, physical activity, body mass and asthma.

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).

Physical activity

Physical activity levels were measured at 100 Hz using ActiGraph GT3X+ accelerometers (Actigraph, Pensacola, FL, USA) worn on the right hip for seven consecutive days. Participants were instructed only to remove the monitor it if they undertook water-based or contact activities, where required. The data were analysed using KineSoft version 3.3.67 (KineSoft, Saskatchewan, Canada) employing 1 second epochs with sustained periods of at least 20-minutes of consecutive zeros considered non-wear time (Catellier et al., 2005). A minimum daily wear time of 10 hours per day for 2 weekdays and 1 weekend day was used (Rich et al., 2013). Physical activity intensities were calculated using Evenson et al. (2008) cut points, which have been shown to be valid and reliable determinats of activity intensity in children and adolescents (Trost, Loprinzi, Moore, & Pfeiffer, 2011).

Lung function

Forced Expiratory Volume in 1 second (FEV_1), Forced Vital Capacity (FVC), FEV_1/FVC ratio, Peak Expiratory Flow (PEF), and Forced Expiratory Flow between 25-75% of vital capacity (FEF_{25-75}) was measured using a portable dry spirometer (Vitalograph, Buckingham, UK). The best of three measurements were taken according to American Thoracic Society guidelines (1995) and to the standardised protocol (Miller, et al., 2005) and expressed as a percentage of the age-sex-stature predicted values dependant on ethnicity (Hankinson, Odencrantz, & Fedan, 1999; Quanjer, et al., 1993; Rosenthal, et al., 1993).

Fractional Exhaled Nitric Oxide

Participants with asthma were asked to perform a Fraction Exhaled Nitric Oxide (FeNO) test, a marker of airway inflammation in asthma, prior to spirometric testing. The FeNO test was performed in a seated position and in accordance with the American Thoracic Society guidelines (Dweik et al., 2011). Participants were asked to exhale away from the device (NIOX MINO, Aerocrine AB, Solna, Sweden) and then inhale to total lung capacity through the device before immediately exhaling for 10 seconds at 50 ± 5 $ml \cdot sec^{-1}$. Visual and audio cues were provided by the computer software throughout. One test was completed and the final three seconds of exhalation were evaluated.

Asthma control

Asthma control was measured using the Asthma Control Questionnaire (ACQ) (Juniper, Gruffydd-Jones, Ward, & Svensson, 2010) which consists of 7-items relating to recent symptoms, medications and FEV_1 score. Each item of the ACQ was scored from 0 to 6 and then averaged to give an overall result. Scores of ≤0.75 or ≥1.5 indicated well-controlled and poorly-controlled asthma, respectively. Internal consistency, measured using Cronbach's alpha coefficients (Cronbach, 1951), for the ACQ were deemed acceptable ($\alpha = 0.77$).

Asthma-related quality of life

The Paediatric Asthma Quality of Life Questionnaire (PAQLQ) was used to assess the symptoms, activity limitations and emotional and environmental effects of asthma (Juniper et al., 1996). The PAQLQ consists of 23 questions (scored on a Likert scale from 1 to 7), with a higher score indicating a better asthma status. 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 (α = 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,

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

Peak $\dot{V}O_2$

Sixty-nine adolescents (39 boys) inclusive of 36 with asthma (21 boys) were selected, using stratified randomisation, to complete incremental ramp tests. The groups were stratified by age, sex and asthma to provide a representative sample of the wider population. Participants performed an incremental ramp exercise test to volitional exhaustion, defined as a drop in cadence >10 rpm for five consecutive seconds, on an electromagnetically braked cycle ergometer (Ergoselect 200, Ergoline GmbH, Lindenstrasse, Germany). The ramp protocol consisted of 3 minutes of "unloaded" pedalling (0 W) followed by an increase in work rate of 12-24 $W \cdot min^{-1}$ dependent on pre-baseline familiarisation incremental ramp tests. Throughout the test, participants were asked to keep the cadence at 75 ± 5 revolutions per minute. Pulmonary ventilation (VE) and gas exchange ($\dot{V}O_2$ and $\dot{V}CO_2$) were measured breath by breath (Jaeger Oxycon Mobile, Jaeger, Hoechberg, Germany).

Data analysis

The peak $\dot{V}O_2$ was taken as the highest 10-second average value attained prior to the end of the test, with the Gas Exchange Threshold (GET) determined using the V-slope method (Beaver, Wasserman, & Whipp, 1986). The interpretation of studies investigating peak $\dot{V}O_2$ is often hindered by not accounting for a possible influence of body size, especially in youth and populations in associated with significant differences in body mass/size. This study includes absolute, ratio-scaled and allometrically scaled peak $\dot{V}O_2$ for comparison with previous studies and to examine 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 ($\Delta \dot{V}O_2 / \Delta W$) 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 by logistic regression adjusting for fitness and time spent in moderate-to-vigorous physical activity (MVPA). Missing data were imputed using multiple imputation for physical activity data, this was done using all other measures for each participant to predict the missing value. All statistical analyses were conducted using SPSS v22 (IBM Corp, Armonk, NY). All data are presented as mean ± standard deviation (SD) where parametric and medians and ranges for non-parametric data with statistical significance accepted as $P < 0.05$.

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 the mean of the PAQLQ is relatively high, 95% scored less than 7 indicating at least some degree of impairment.

In contrast to the 20-metre shuttle run in which healthy participants completed significantly more shuttles than those with asthma (48 ± 24 vs 42 ± 23 shuttles, respectively), peak $\dot{V}O_2$ and scaled peak $\dot{V}O2$ did not differ according to asthma status (Table 3). Similarly, there were no significant differences between asthma and non-asthma groups in the absolute or relative GET or the gain. However, participants with asthma did have a significantly shorter MRT_T, although these differences were not observed below the GET and were ameliorated once work rate was added as a covariate.

Although significant differences were shown between girls and boys for cardiorespiratory fitness and physical activity levels, sex did not account for any of the variance between asthma and non-asthma groups. Therefore, boys and girls were pooled for all subsequent analyses. The number of shuttles completed in the 20-metre shuttle run was negatively correlated with BMI ($r = -0.34$, $P < 0.05$) and positively associated with MVPA ($r = 0.34$, $P < 0.05$) pooled for both those with and without asthma. Body mass index was also negatively associated with MVPA ($r = -0.18$, $P < 0.05$). Positive associations were shown between cardiorespiratory fitness according to both the 20-metre shuttle run and peak $\dot{V}O_2$ and ACQ ($r = -0.15$ and -0.35; $P < 0.05$), PAQLQ ($r = 0.27$ and 0.34, $P < 0.05$) and PedsQL ($r = 0.22$ and 0.35, $P < 0.05$). Furthermore, participants without asthma reported a significantly higher quality of life (78.2 ± 14.7 vs 74.4 ± 17.8). Whilst significant, these correlations are weak and should be interpreted with caution.

As BMI, 20-metre shuttle run and MVPA were significantly different between the asthma and non-asthma groups, univariate logistic regression analyses were performed on each. Both BMI and fitness were shown to be significantly associated with asthma; MVPA failed to reach significance (P = 0.06) even when using multiple imputation to replace missing MVPA data. Multivariate logistic regression (Table 4) revealed BMI as an independent factor associated with asthma.

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, 2000). Furthermore, the discrepancies in the 20-metre shuttle run between participants with and without asthma may have been due to EIB limiting some participants with asthma, possibly resulting in the early dropout from the measure. The lack of effect of asthma on peak $\dot{V}O_2$ in the present study agrees with previous studies (Berntsen et al., 2009; Pianosi & Davis, 2004; Santuz et al., 1997) and suggests that previous studies utilising indirect estimates of cardiorespiratory fitness may have drawn erroneous conclusions (Cairney et al., 2008; McNarry et al., 2014), as would also have been done according to the current 20-metre shuttle run results. The relatively low peak $\dot{V}O_2$ values (Rodrigues, Perez, Carletti, Bissoli, & Abreu, 2006) reported in this study nonetheless highlight an area of concern with regards to the current health of adolescents (Ortega, Ruiz, Castillo, & Sjostrom, 2008). Indeed, considering that peak $\dot{V}O_2$ is one of the strongest predictors of all-cause mortality (Kodama et al., 2009), with a strong relationship between peak $\dot{V}O_2$ as a child and adult (Malina, 2001), the current results highlight the need for interventions that successfully, and sustainably, increase the cardiorespiratory fitness of youth.

This is the first study to consider the influence of asthma on the sub-maximal parameters of aerobic fitness (MRT, gain and GET), many of which have been suggested to be more sensitive to both advantageous and deleterious adaptations than peak $\dot{V}O_2$ (McNarry, Harrison, Withers, Chinnappa, & Lewis, 2017). However, in agreement with peak $\dot{V}O_2$, no influence of asthma was manifest on any parameter of aerobic fitness. Whilst other respiratory diseases have been found to be associated with significant differences in gain between those with and without the condition (Fielding et al., 2015), participants with asthma were not different to their peers. These findings suggest that adolescents with asthma do not engender a greater O_2 cost of exercise in comparison to their peers. The findings on the GET suggest that those with asthma are able to participate in similar training programmes as those without. Although optimal training should be based on an individuals' GET, as differences were not shown, those with asthma will have comparable training "zones" that should elicit similar improvements. These findings are in accord with previous research showing no differences between asthma and their healthy counterparts (Santuz et al., 1997). Whilst the GET was low in comparison to previous findings (Fawkner and Armstrong 2004), the results do not suggest deconditioning (<50% peak $\dot{V}O_2$) (Urquhart & Vendrusculo, 2017). In contrast, it is perhaps interesting to note the significantly longer MRT found here than in previously reported research (Barstow, Jones, Nguyen, & Casaburi, 2000; McNarry, Welsman, & Jones, 2011), which may suggest chronic deconditioning and agreeing with the relatively low peak $\dot{V}O_2$ values observed from the cycle ergometer. These findings must be interpreted with caution however due to the influence of ramp rate on the MRT which limits inter-study comparisons (Boone, Koppo, & Bouckaert, 2008). The lack of a difference between adolescents with and without asthma in peak $\dot{V}O_2$ and subsequently the MRT suggests that any derangements in airways of the participants with asthma do not affect the O_2 delivery to the mitochondria within the muscle.

In agreement with previous studies (McNarry et al., 2014; Vahlkvist, Inman, & Pedersen, 2010), the prevalence of overweight and obesity in the present participants with asthma was high in comparison to their peers. Whilst the causal relationship between asthma and obesity remains unclear, postulated mechanisms include co-morbidities or mechanical effects of an increased pressure caused by excess tissue mass in the abdomen and chest influencing hyper-responsiveness or symptoms of 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 having asthma to participate in the study. The lack of difference between participants with mild and moderate or severe asthma may be due to the study not being powered for subgroup analysis by severity. In addition, there may have been a self-selection bias such that participants with more severe asthma and/or poorer fitness may have chosen to opt out of more vigorous subsample testing (n = 3). Finally, the different modalities of the field and lab-based measures of cardiorespiratory fitness limits our interpretation to some extent. Whilst a treadmill may have been more comparable to the 20-metre shuttle run test, the cycle ergometer was used for the pragmatic reasons, participant familiarity and to reduce movement artefact for other measures not associated with this manuscript.

Conclusion

In conclusion, adolescents with predominantly mild persistent asthma do not differ in cardiorespiratory fitness from their peers, however, they do have an increased BMI and engage in less MVPA. The present findings also highlight the importance of using appropriate measures of cardiorespiratory fitness to determine the influence of disease on exercise responses. Finally, although only a weak relationship was found between cardiorespiratory fitness and quality of life, further studies should investigate if cardiorespiratory fitness can reduce asthma severity in adolescents with more severe asthma.

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Table 1. Anthropometric measures for participants with and without 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*

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

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

Mean±SD or median (range); * = Significant p<0.05; NA = Not applicable; MPA = moderate physical activity; VPA = Vigorous physical activity; MVPA = Moderate-to-vigorous physical activity; %Predicted = Expressed as a percentage of the age-sex-stature predicted value; FEV_1 = Forced Expiratory

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

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

	Asthma	Non-asthma	P-value
Baseline $\dot{V}O_2$ ($l{\cdot}min^{-1}$)	0.60 ± 0.10	0.60 ± 0.10	0.70
$\dot{V}O_2$ peak ($l{\cdot}min^{-1}$)	2.00 ± 0.50	2.10 ± 0.50	0.67
$\dot{V}O_2$ BM ($ml{\cdot}kg^{-1}{\cdot}min^{-1}$)	36.9 ± 8.3	41.1 ± 7.4	0.02*
$\dot{V}O_2$ Scaled ($ml{\cdot}kg^{-0.57}{\cdot}min^{-1}$)	205.1 ± 43.6	221.6 ± 38.6	0.11
GET ($l{\cdot}min^{-1}$)	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 ($ml{\cdot}min^{-1}{\cdot}W^{-1}$)	9.0 ± 1.8	9.1 ± 2.8	0.78
S_2 Gain ($ml{\cdot}min^{-1}{\cdot}W^{-1}$)	10.8 ± 2.0	11.0 ± 1.3	0.55
S_T Gain ($ml{\cdot}min^{-1}{\cdot}W^{-1}$)	10.0 ± 1.5	10.3 ± 1.4	0.49

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

Table 4. Logistic regression analysis to test potential association with asthma from Body Mass Index, Moderate-to-Vigorous Physical 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

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