Changes in breathing reserve and expiratory flow limitation at peak exercise intensity after a 10-weeks exercise intervention in adolescents with asthma

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Preface/Acknowledgements

Dear dad. When you were alive, you inspired me to chase my dreams. You still do, even though you are not among us anymore. Thanks for being a loving, funny, kind, inspiring and encouraging dad, which I have many good memories from. Dear mum, little sister, brother-in-law, and boyfriend. Thank you all for being so supportive, understanding, caring, loving, funny and making me feel loved.

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1 Part 1 Introductory review

1.1 Sammendrag

Formål: Denne masteroppgaven har som hensikt å se på i hvilken grad pustereserve og luftstrømsobstruksjon ved maksimal belastning hos ungdommer med astma forandrer seg fra før til etter en treningsintervensjon. **Teoretisk forankring:** Trening kan være bra for ungdom med astma med tanke på psykososial funksjon, livskvalitet og kardiorespiratorisk form. Imidlertidig gir også ungdommer med astma uttrykk for å oppleve pustebegresninger under trening, og at pustebegrensningene kan hindre dem i trening. Det er imidlertid begrenset kunnskap om hvordan pustemekanismen fungerer under maksimal belastning. **Metode:** 15 ungdommer (13-18 år) med astma gjennomførte en 10 ukers treningsintervensjon med varierte kondisjonsaktiviteter. Oppmøte og pulsregistrering fra hver treningsøktene ble registrert. Deltakerne ble testet før og etter intervensjonen på laboratoriet. Lungefunksjon ble målt med spirometri. Peak oksygenopptak (VO_{2peak}) ble målt under en kardiopulmonal belastningstest (CPET) på tredemølle. I tillegg ble intrabreath (IB)-målinger målt under VO_{2peak}.. Graden av luftstrømsobstruksjon (EFL) ble definert ut ifra der hvor tidevolumet (extFVL) møter eller overstiger den forserte ekspiratorisk kurven (MFVL) fra hvile. Grunnet skjevfordelte data, ble en ikke-parametrisk statistisk test (Wilcoxon) brukt for å sjekke endring i variablene fra før til etter treningsintervensjonen. Spearman's rho ble brukt for å regne ut korrelasjon mellom variablene. Resultater er presentert som median med interkvartil bredde (IQR). **Resultater**: Luftstrømsobstruksjon hos ungdommene med astma var før treningsintervensjonen 0.0 % (23) og 0.0 % (0.0) etter treningsintervensjonen. Pustereserven hos ungdommene med astma var -0.6 % (15.6) før og 0.5 % (13.2) etter intervensjonen. VO_{2peak} var 39 ml/kg/l/min (16.2) hos ungdommene med astma før treningsintervensjon og 42.6 ml/kg/min (19.5) etter treningsintervensjonen. Negativ korrelasjon mellom pustereserve på ρ= -0.4) og luftstrømsobstruksjon ble funnet, samt negativ korrelasjon mellom luftstrømosobstruksjon og VO_{2peak} (ρ=-0.4). Peak minuttvolum (VE_{peak}) hadde en korrelasjon på ρ=0.1 med luftstrømsobstruksjon. Pustereserven og VE_{peak} hadde en korrelasjon på ρ= 0.3. Alle korrelasjonsverdiene var ikke-signifikante. **Konklusjon:** Det kan tyde på at ungdommene med astma ikke har luftstrømsobstruksjon, og at de fortsatt har lav pustereserve, etter 10 ukers treningsintervensjon.

Nøkkelord: Astma, trening, pustebegrensning, luftstrømsobstruksjon, pustereserve, ungdommer, kardiopulmonær belastningstest

1.2 Abstract

Purpose: The aim of the study is to assess to what extent the breathing reserve (BR) and expiratory flow limitation (EFL) at peak exercise measured at peak oxygen uptake (VO_{2peak}) change after an exercise intervention when compared with the baseline assessment in adolescents with asthma. **Literature framework:** Exercise is safe and beneficial for youth with asthma, in relation to psychosocial functioning, quality of life, and cardiorespiratory fitness. However, we also know that adolescents with asthma experience perceived breathlessness and dyspnea during exercise. There are few studies which investigate the ventilatory changes in adolescents with asthma at VO_{2peak}. **Method:** Fifteen children, aged 13-18 years, participated in an exercise intervention with various endurance activities for ten weeks. The data analyses included pre- and post-testing, attendance rate, and HR-monitoring during each session. Significance of variables before and after the exercise intervention was calculated by using Wilcoxon and correlation was checked using Spearman's rho due to skewed data. Results are presented as median with interquartile range unless otherwise stated (IQR). **Results:** There was no change in EFL from before (0.0 % [23]) to (0.0 % [0.0]) at post-assessment. BR was -0.6 % (15.6) before and -0.5 % (13.2) at post-assessment. Peak oxygen uptake (VO_{2peak}) was (39 ml/kg/min [16.2] before to (42.6 ml/kg/min [19.5]) at post-assessment. There was a negative correlation of ρ=-0.4 between BR and VO_2peak at post-assessment.$VO_{2\ peak}$ showed also a negative correlation with EFL of ρ= 0.4 at post-assessment. Minute volume (VE) showed a correlation of ρ=0.1 with EFL while BR and VE_{peak} had a correlation of ρ= 0.3. All correlation values were non-significant at the post-assessment. **Conclusion:** The findings indicate that there is no EFL before or after and that BR remains low after the 10-week exercise intervention, in adolescents with asthma at VO_{2peak}.

Keywords: Asthma, exercise, ventilatory limitations, expiratory flow limitation, breathing reserve, extFVL/MFVL-analysis, exercise physiology, cardiopulmonary exercise testing

Abbreviations

EFL: Expiratory flow limitation

BR: Breathing reserve

PA: Physical activity

BHR: Bronchial hyperresponsiveness

EIB: Exercise-induced bronchoconstriction

extFVL: tidal exercise flow-volume loop

MFVL: maximal flow-volume loop**CPET**: Cardiopulmonary exercise test

VE: Minute ventilation

MVV: Maximal voluntary ventilation

FEV_1: Forced expiratory volume in 1 second

FVC: Forced vital capacity

BF: Breathing frequency

VC: vital capacity

VE: minute ventilation

VO_2: oxygen uptake

$VO_{2\text{-peak}}$: Highest VO_2 achieved on a test performed to limit tolerance

VE/VCO_2: Ventilatory equivalent for VCO_2

VT: tidal volume

EILV: End- inspiratory lung volume

EELV: End-expiratory lung volume

IC: inspiratory capacity

ATS: American Thoracic Society

ICON: International consensus on Pediatric Asthma

2.0 Introduction

2.1 Structure of the article-based master thesis with an introductory review

The thesis is comprised of three parts. Presented first (part 1) is the introductory review, which expounds on the theme, aim, research questions, hypothesis and relevance of the study within health research. Strength and limitations of this study as well as statistical and ethical consideration will also be further explained here. In part 2, the article written for publication in BMJ Open Respiratory Research follows. Note that the presented article is subject to further editing and does not necessarily represent the final version for submission. Also, note that the presented co-authors in the article version are presented along as if the article was sent in already. The result will only be presented in the following article. There, results will be analyzed together with the earlier theory and research in the discussion chapter, followed by the conclusion. Figures follow the reference list for the article, in line with submission guidelines for the journal. Last, several appendices relevant to the introductory review follow (part 3).

2.2 Why assessment of expiratory flow limitation and breathing reserve at peak oxygen uptake in adolescents with asthma is necessary

According to the international consensus on pediatric asthma, (ICON) asthma can be defined as

> […] a chronic inflammatory disorder associated with variable airflow obstruction and bronchial hyperresponsiveness (BHR). It presents with recurrent episodes of wheeze, cough, shortness of breath and chest tightness (1, p. 33).

Currently, there is no nationwide study of the prevalence of asthma in Norway (2). However, in a cohort with children from Oslo, 20 % had asthma around 10 years of age. The prevalence of asthma increased to 26 % around 16 years of age (3,4). Asthma in childhood is a heterogeneous disease with different and variable symptoms depending on the age, gender, genetic background and environmental influences of the patient. Hence, several mechanisms can influence and trigger asthma (5).

One aim of treatment to achieve control of the disease is to use the least possible amount of medication (1). If asthma control is not achieved after controlling for medication compliance, environmental control, treatment for comorbid rhinitis, etc, stepping up medication should be considered (1). In addition to medical treatment, avoiding triggers for the disease can have beneficial effects on the activity of the disease. However, completely avoiding all allergens is usually impractical or impossible, and may have the added disadvantage of limiting the patient in daily life (1). Exercise has been shown to be useful for supplementary treatment of asthma (6). However, exercise can also trigger asthma; so-called exercise-induced bronchoconstriction (EIB) (7). EIB usually occurs a few minutes after exercise. It is defined as reversible narrowing of the airway, resulting in shortness of breath (8). EIB can be used to measure the BHR and can be a marker of asthma before the clinical diagnosis of asthma has been made (9). According to the American Thoracic Society (ATS) guidelines, EIB is defined as a drop of $\geq$10 % in FEV_1 after exertion on an exercise test (10). EIB occurs more often in children and adolescents (7). In a global perspective, EIB and exertional dyspnea occur in 9% of children and adolescents (11).

Symptoms of asthma can be one of the barriers to physical activity (PA) due to avoiding dyspnea, breathlessness in exercise, and are affecting more and more children and adolescents as the prevalence of asthma increases (7,12). According to Del Giacco, Firinu, Bjermer et al., there is a tendency for low participation in PA and physical play in children with asthma, which could have the possible consequence of negatively impacting the daily life quality in those children (7). People with asthma tend to report that they are symptomatically better when fit, however, the physiological basis of dyspnea has not been systematically investigated

yet (13). How expiratory flow limitation (EFL) influences exercise or contribute to perceived dyspnea is unclear (14). When defining and quantifying EFL, the constraint can be defined in degrees of limitation such as no or minimal, mild, moderate or severe limitation, rather than all-or-nothing phenomena (11). Reduced breathing reserve (BR) (<15%) at peak oxygen uptake (VO_{2peak}) can also indicate a ventilatory limitation in adolescents but can also indicate that they use more of their ventilatory capacity (VC) (15). Whether BR in adolescents with asthma contribute to exercise limitation remains unclear.

Concerning ventilatory changes at maximal exertion, few studies have examined this, especially how BR and EFL at peak oxygen uptake (VO_{2peak}) change in adolescents with asthma before to after an exercise intervention. Through assessing changes in EFL and BR, one can assess how these contribute to ventilatory limitation during exercise (14). According to ICON, there is a need for adjusting the recommendations for physical activity in the asthmatic treatment of the pediatric age group (1).

2.3 Aim of this study

The aim of this study is to assess EFL and BR at VO_{2peak} before and after a 10-week exercise intervention in adolescents with asthma.

2.4 Research question

The research question is:

- to which extent do BR and EFL at VO_{2peak} change after 10-week exercise intervention in adolescents with asthma compared with baseline assessment?

2.5 Priori hypothesis

H_0: There are no changes in BR and/or EFL under VO_{2peak} at post-test compared by baseline assessment

H_1: There are changes in BR and/or EFL at VO_{2peak} at post-test, compared by baseline assessment.

3.0 Theoretical background

3.1 Ventilatory function

Ventilation is the process that provides oxygen (O_2) to the tissues in the body and removes carbon dioxide (CO_2) from the body. The body and its cells need a steady supply of O_2 to survive and work. Ventilation is also needed to remove CO_2 from the body since CO_2 is a waste product of the metabolic process. Expiration means breathing out, while inspiration means breathing in (16).

3.1.1 Cardiopulmonary variables measured during exercise

Whether or not a persons ventilatory or cardiological functions are limited during exercise, can be measured during a cardiopulmonary exercise test (CPET) (15). CPET is an ergospirometric test with measurement of gas exchange; oxygen uptake (VO_2) and carbon dioxide (VCO_2) in expirated air. CPET can be performed on a treadmill or an ergometer cycle. It is common to use test protocols with gradually increasing effort and lasting 8-12 minutes. The treadmill is motor-driven and introduces progressively increasing stress on the individual as the speed and incline of the treadmill rises (10).

The frequency of breathing per minute is called the breathing frequency (BF). The volume of expired air from the lungs during one minute is called the minute ventilation(VE), while the volume of air that is inspired or expired of each breath is called the tidal volume (VT). The volume expired from a maximal inspiration is called the vital capacity (VC) (10). Inspiratory capacity (IC) is the volume of air a person maximally can inspire when the person fully inspires with no stop after passive expiration(17). End-expiratory lung volume (EELV), is the volume of air remaining of the expired breath of the end the VT. The volume of air that is filling the lungs, is called the end-inspiratory lung volume (EILV) (10,11). The ratio of VE to VCO_2 is called the ventilatory equivalent for CO_2 (VE/VCO_2) (10).

$VO_{2\text{-peak}}$ is the highest volume of oxygen uptake that the subject has performed to the limit of tolerance. $VO_{2\text{-peak}}$ is expressed in liters per minute and is often adjusted for body weight (12). Help criteria such as plateauing of VO_{2peak}, achieved maximum heart rate, and a Borg Scale >17, and values over 1.15 are more likely to associated with maximum effort (10).

3.1.2 Measurement of lung function

The forced expiratory capacity (FVC) is the volume of air that can be forcibly expirated after a full inspiration. FEV_1 is an abbreviation for the forced expiratory volume in one second, which is the volume of air expiration of the first second of the FVC-maneuver (10,17). FVC and FEV_1 can be expressed in absolute values and given in liters, or as a percentage of predicted values, which are corrected for sex, age, height, and ethnicity(10,17-18). The FEV_1/FVC ratio represents how much of the persons vital capacity they are able to expire in the first second of forced expiratory expiration (FEV_1) to the full forced vital capacity (19) Both FEV_1 and FVC are measured using spirometry and at rest (17).

3.1.3 Measurement of maximal voluntary ventilation and BR

The maximal volume of air that the person can breathe is called the maximal voluntary ventilation (MVV). According to the American Thoracic Society (ATS), MVV can be measured either directly for 10 seconds expressed in units of liters per minute or estimated by multiplying FEV_1 with 35 (10). MVV can be used to calculate BR at VO_{2peak}. When calculating the used percentage of MVV, one divides VE at VO_{2peak} with MVV. Thereafter, BR can be calculated by subtracting 100 from the used percentage of MVV. BR represents the remaining respiratory capacity, often presented in percentage of the MVV(10).

3.1.4 Measurement of EFL

With a spirometer turbine which is attached to the CPET while running, measurement of flow limitation can be done. EFL is defined by Johnson as the tidal exercise volume loop (extFVL) that meets or exceeds the maximal flow volume loop (MFVL) (20). While the term extFVL is used for the tidal exercise flow-volume loop, meaning the exercise tidal volume loop of the volume that is produced during exercise, the MFVL represents FVC(20).

3.2 Ventilation during exercise in without having asthma

Usually, BF should increase during exercise. It is mostly the VT that increases ventilation during the low level of exercise. When exercise demand progresses, both the VT and BF increase until 70-80% of VO_2peak is achieved, thereafter the BF continues to rise (10,20). VT usually reaches its plateau level at 50-60% of the VC. BF increases in both untrained adolescents and athletes (20).

When VE increases exponentially to the increase in VO_2 in CPET-testing, is when the ventilatory threshold is met (10). The increase of lactate will stimulate the production of CO_2, in terms of VE (10). A higher ratio than >34 of VE/VCO_2 at the ventilatory threshold can indicate poor ventilatory efficiency, while <30 at the ventilatory threshold is normal (14). The ratio of VE/VCO_2<36 at VO_{2peak} is considered normal, while values <36 are considered pathological according to ATS (10).

Normally, EILV increases in individuals without asthma when exercise demand progress, as the exercise intensity and VE increases. As the exercise intensity and VE increases, the EELV continues to fall (20).

At peak exercise intensity, one VO_{2peak}. When VO_{2peak} is achieved, one would expect that people without asthma with normal cardiorespiratory fitness usually have around 20-40 % BR (15). A 20-40% BR could indicate no ventilatory restriction to exercise. However, it is not uncommon that trained people without asthma have a low BR if they use nearly all of their VC (15)

3.3 Ventilation during exercise while having asthma

The VC is reduced in people with EFL (20). Due to the early onset of EFL, EELV may increase with even light activity. An increase in EELV can indicate hyperinflation (20). However, we do not yet understand fully the mechanism by which EELV rises (20). The increase of EELV increases the work and oxygen cost of breathing and decreases the endurance of the inspiratory muscle, and could increase the BF. As BF increases during exercise due to higher ventilatory demands, this can cause a further increase in the EFL (14, 20).

The increase in EELV that occurs with EFL decreases optimal inspiratory muscle length and increases the work and oxygen cost of breathing (20, 21). Furthermore, the increased EELV and the following constraint of VT increase could possibly contribute to EFL in people with lung disease (20). Figure 1 below shows possible changes of EELV, EILV, and EFL from rest to exercise.

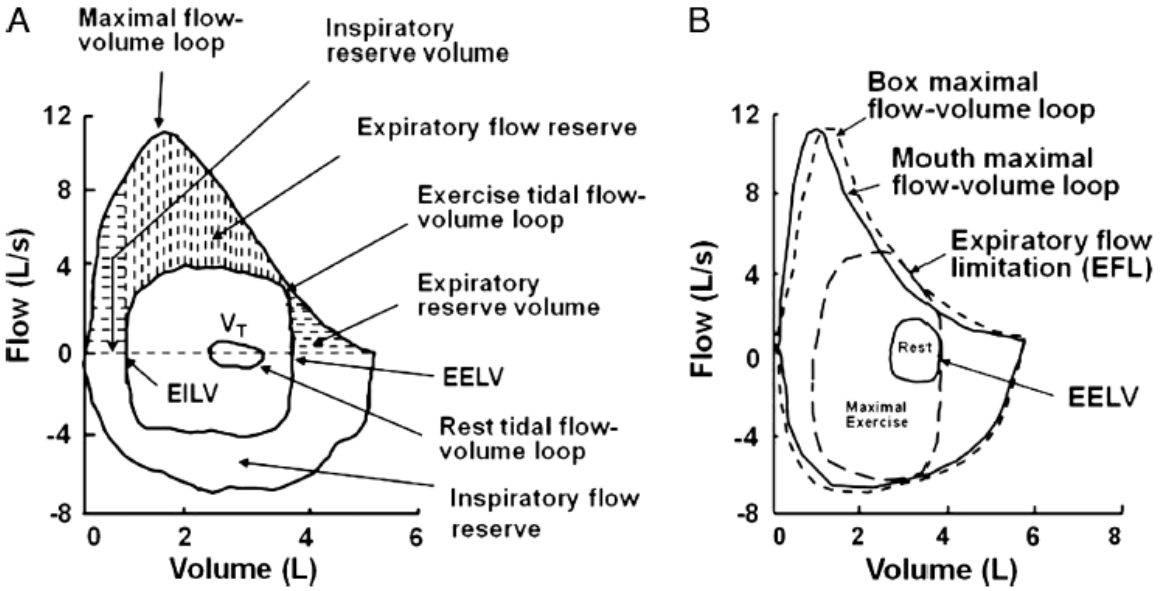

Figure 1.Ventilatory changes from rest (A)to exercise (B). Taken with permission from *Exercise and Sport Sciences Reviews*, Volume 41 Issue 1. Tony Babb. Exercise Ventilatory Limitation: The Role of Expiratory Flow Limitation. p. 14. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3529766

At $VO_{2peak,}$ the percentage of BR could be low (<15 %) and indicated that people have a ventilatory limitation to exercise (15). However, it is possible that also that trained people with asthma have a low BR if they use nearly all of their VC (15).

The ventilatory efficiency is reduced by an increased VE in people with mild to moderate EFL. MVV and VE are described together as the dyspnea index (VE/MVV), a ratio given for a particular workload, whereas an increased ratio of dyspnea index could affect exercise tolerance. Dyspnea index can reflect limitation during exercise when MVV is low and when VE is high (22). Several studies have demonstrated an association between dyspnea intensity during exercise and that dyspnea can be an indication of lung hyperinflation (20).

3.4 Previous research on exercise and bronchial hyperresponsiveness

Schichlone, Morici and Zangla reports that exercise can have a beneficial role in asthma treatment and asthma management, for reducing the BHR in adults with asthma (23). Ram, Robinson, and Black support this as well (24). BHR was decreased after the exercise intervention for mild untreated adults with asthma in the study of Hallstrand, Bates, and Schoene (22). Wanrooj, Willeboordse, Dompeling et al. also concluded that exercise has positive effects on cardiorespiratory fitness in children and adolescents and that exercise reduces BHR. The reason for this, is the lower VE among children with better cardiorespiratory fitness, will have for a given workload (8). Decreased BF after the exercise intervention in adults was also seen in the study of Hallstrand, Bates, and Schoene (22). Hallstrand, Bates, and Schoene demonstrated a decrease of hyperpnea in exercise in adults due to increased ventilatory efficiency (22) Increased BF could probably stimulate the EIB, so a lower VE is, therefore, beneficial (8,22). Exercise for individuals with asthma is considered safe (8,10).

4.0 Extended discussion:

4.1 Statistical considerations

Baseline characteristics in table 1 and the main results in table 2 in the article are given as median values with interquartile range (IQR) due to skewed data. When using IQR, one uses the range between the 25% lowest and 25 % highest values middles score rather than the extreme scores (25). IQR is, therefore, less affected by extreme scores than if one uses minimum and maximum values for dispersion measure. Hence, IQR as useful for skewed data (25). Use of the median for describing the central tendency of the data is also more robust since extreme values can influence the mean value more (26). Non-parametric tests were used for analyzing differences between pre and post measurements, due to the skewed distribution of data. In addition, a low sample size as in our study (n=15) often requires non-

parametric testing since extreme values will make a bigger impact on a small group. It is usual to use a non-parametric test when the sample size is below 30 (26). Non-parametric statistical tests are more robust than parametric tests since these are less affected by extreme values. Correlation values in table 3 in the article are given with Spearman's rho (ρ). Munros descriptive terms for the strength of correlation coefficients have been used to interpret the strength of the relationship between variables (26). Categorical variables (gender) are presented as frequencies and percentages.

The statistical methods used to test change from pre to post measurements were the Wilcoxon Signed Rank Test, which one uses for dependent continuous variables, for comparing two related samples (26). Wilcoxon Signed Rank Test is a non-parametric alternative to the paired t-test (26). BR and EFL were all measured at VO_{2peak} are all dependent since we are investigating whether these variables change due to the exercise intervention. Of the same reason, MVV, FEV_1, FVC, VE, dyspnea index, VE/VO_2 VE/VCO_2 and $VO_{2\ peak}$ is also considered as dependent variables. P-values <0.05 was considered as statistically significant. That means that we can accept a margin of error of 5%, a 5 % probability that our statistical conclusion is wrong. Occasionally a more stringent level of 0.01 is used, for example when the consequences for making wrong clinical decisions cause severe effects on health (26), which is not the case is this present study.

All test were two-tailed, for the possibility of testing the relationship between variables in both directions (26). These variables were VE_{peak} and EFL, EFL and $VO_{2\ peak}$ and BR. All correlation variables that were checked, were at VO_{2peak} at the post-test, after the exercise intervention.

4.2 Reliability and validity of the measurement of extFVL/MFVL-analysis during exercise

Few studies exist concerning the reliability and validity of the extFVL/MFVL-analysis. However, there are some things that can affect the reliability of the extFVL/MFVL-analysis such as placement of extFVL within MFVL (20). If the IB maneuvers are not correctly done,

this can give a false presentation of the EFL. If the person is not fully inspirating, this will cause the extFVL to be smaller and shifted more to the left within the MFVL, underestimating the EFL of the adolescents with asthma. Hence, practicing IB maneuvers is critical for the reliability of the EFL/MFVL-analysis (20). According to Johnson, for most patients, it is likely that adequate IB maneuvers can be performed during exercise if enough time is spent prior to exercise practicing IB-maneuvers (20). Another critical issue regarding reliability is whether the computer understands when the IB maneuvers are done. Therefore, IB maneuver was manually checked in addition.

4.3 Reliability and validity of methods of calculating BR

Since FEV_1, correlates with MVV (17), one can use FEV_1 x 35 to estimate MVV, but Hallstrand suggests that subtle changes in lung function or airway reactivity not always can be detected by the FEV_1 maneuver (17,22). However, using directly measured MVV has shortcomings for assessing ventilatory limitation (20). First, there are significant differences in breathing pattern for the MVV and the hyperpnea which is reflex-driven in the exercise, since it not represent the typical breathing pattern during exercise (20). Klas and Dempsey demonstrated in 1989 the work of breathing (WOB) was higher in MVV than the hyperpnea during exercise (27), as shown in figure 2 below. When maximal flow rates were achieved for brief periods via the MVV maneuver, the EELV was high, and therefore the ventilatory work greatly exceeded that achieved in peak exercise intensity (27). Since one cannot do MVV over 15 seconds, this confirms the excessive work and cost which is not needed in exercise. Second, the MVV only measures the maximal capacity for the lungs and does not give any specific information about what type of ventilatory constraint there is, such as inspiratory flow, high inspiratory elastic load or EFL (20). Third, the MVV is also motivationally dependent, and whether there is a consistent relationship between the exercise ventilation and MVV to influence the perception of dyspnea of exercise tolerance, is yet to be further examined (20).

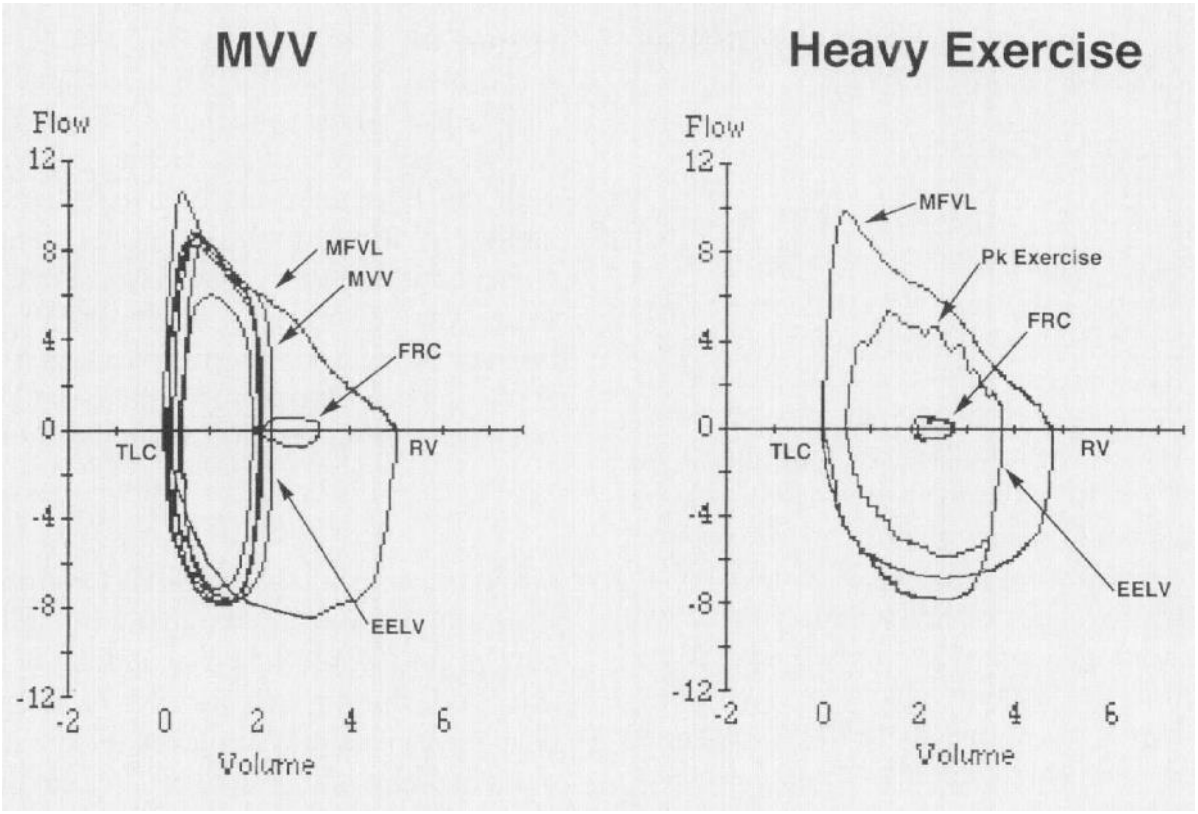

Figure 2: The difference in breathing pattern and EELV when the MVV maneuver is performed (left) relative to the same persons at peak exercise intensity (right). Reprinted from CHEST. Bruce D. Johnson, Idelle M. Weisman, .Jorge R Zeballos, Ken C Beck. Emerging Concepts in the Evaluation of Ventilatory limitation During Exercise: the exercise tidal flow volume-loop. Volume116, Issue 2 p. 493 Copyright (1999) with permission from Elsevier.

4.4 Strength and limitations of the study

80% of all included participants at baseline completed the entire intervention, which counts a strength. Another strength with the study, is the use of extFVL/MVFL-analysis when assessing EFL at VO_{2peak}, where one can extract more information from the flow curves, such as; 1) the degree of EFL, since EFL is not an "all or nothing" phenomenon, 2) the curves shows us breathing strategy, such as changes in the EELV 3) elastic load, represented by EILV (EILV/TLC or the VT relative to the IC (20). ExtFVL/MFVL-analysis gives basically a good visualization of how much of the amount of VC which is utilized and how great BR which potentially can be increased (20). Plotting the extFVL with the MFVL gives a quantification of the sources of mechanical constraint and it not as motivationally dependent as the MVV maneuver, which adds more information during CPET, such as BF and VT (20).

However, the use of extFVL/MFVL-analysis can also be seen as a limitation, because extFVL/MFVL-analysis is not an established method and there exist no studies to compare with (20). Hence, results which are considered normal is yet unclear. The extFVL/MFVL-analysis is also subjective because considering the extent of EFL is dependent on the accuracy of the person evaluating the results from the extFVL/MFVL-analysis (20). Plotting of extFVL within MFVL is also done manually and therefore, non-accuracy with measurement can influence the reliability of the measurement. A limitation with extFVL/MFVL-analysis is the quality of the IB maneuvers, and whether the recordings represent the full IC of the person (20). Plotting extFVL/MFVL-analysis makes testing and analysis more complex due to the management of several variables at once. Also, technical accuracy is dependent on the assessment of extFVL/MFVL-analysis (20). Estimating the MVV for calculation of BR through multiplying FEV_1 with 35 is also seen as a reliable and reproducible method (17).

CPET is a gold standard for evaluating exercise intolerance with lung diseases, according to Palange et al, but should be used together with spirometry for diagnostic purposes (28). VO_{2peak} was used instead of VO_{2max}, so participants that did not meet VO_{2max} criteria did not have to be excluded from the analysis when there from before were few participants in our study. When using the term VO_{2peak}, there a no need for evidence of plateauing, which one will need to determine when using VO_{2max} is reached (10). Children often do not manage to achieve a plateau in VO_2 despite signalizing that they have reached their limit of tolerance. Hence, using VO_{2peak} as a term will be more suitable(29).

Using BMI z-score instead of BMI-cut offs can be considered as a strength since they are more suitable for adolescents. The widely used BMI cut off for overweight, obesity, and thinness, are based on and linked to adults BMI-cut offs (30).

The main limitation was the small study sample size since the sample size cannot be used in an effect-study (26) Representativeness is harder to achieve with low sample size(26). Since most of the adolescents in this study had well-controlled asthma, the findings of the main study are less representative for other adolescents with less-controlled, moderate or severe asthma. EFL and BR could have been worse in groups with less-controlled asthma and moderate or severe asthma.

Due to the single group design and low sample size, there is no chance for random allocation of participants into several groups, nor is there an opportunity for a comparison of EFL and

BR between adolescents with asthma and adolescents without asthma (26). Often, this type of design with no comparison or random allocation of participants between several groups is considered a "weak" research design (26). When the sample size is small, this can higher the probability of type two error, meaning no detection of changes when there, in reality, are changes (26). However, low sample size and design can be appropriate for this type of study. Few studies assess changes in EFL and BR in adolescents with asthma. When few studies exist, doing research with a low sample size first before conducting random controlled trials (RCT) is preferable so that unnecessary recourses in terms of time, subjects and financial cost can be avoided in a RCT. We tried to recruit several participants in this study, but recruiting was difficult. Several potential participants were occupied with school and other activities to and declined to participate.

Some participants had to stop before reaching full exhaustion at the post-test. This can be a limitation for the study since this can influence the results in terms of no improvement of $VO_{2peak,}$ which is strange after an exercise intervention. However, the reasons for early termination of CPET was to avoid injuries due to stumbling. Safety of the participants during testing should always be prioritized. Another reason for early termination CPET was that participants were not motivated to run to full exhaustion due to pain in legs while running. As test leaders, we could only encourage, not force, adolescents, to run until full exhaustion.

4.5 Ethical considerations

PLAY has been approved of the Regional ethics committee (REK no: 2017/1320). Name of the participating adolescents and identification code looked down separately. Data were de-identified before plotted into SPSS.To ensure informed consent, potential participants and their parents got a written letter about participation when they were recruited (appendix 2a and 2b). In this letter, adolescents got information about the background and aims of the study, what the participation would mean for them, and the potential benefits and costs with joining the study. Adolescents were also informed that participation was voluntary and that they could decline from the project without consequence for treatment. It was mentioned that the results will be treated anonymously, and they had the right to get information about the results of projects. For all participants, we received a signed consent form from participants and their parents (appendix 2a-b). Participants over 16 years old were first contacted before

parents, as they possess the right to give consent according to Norwegian law (31) For participants under 16 years old, the parents were contacted first.

Based on previous experiences and research concerning the exercise and the intensity level that was tested, adolescents did not have any risk of injury, pain or mental strain (8,10). However, children and adolescents may be considered as vulnerable research participants need for extra protection and support (32). Before each session adolescents were instructed to use asthma medication, as prescribed by their doctor. For safety reason, nebulizer and extra asthma medication were available. Instructors were supervised in use of these. The exercise was done with two instructors making sure the training was safe, and during the opening hours of the training facilities if case extra assistance was needed. The instructors were supervised on how to give extra rescue medicine and there was always extra medication available if needed, such as a nebulizer, an aero chamber and Ventolin. Participation in the study was of no greater risk than in daily life for adolescents with asthma. The CPET is a safe type of test, where the risk of death for patients between 2 and 5 per 100 000 exercises done(10). Testing and exercise in the intervention were done with safety supervision and after strict safety procedures, and therefore a small risk of harm for participants. Only research members who were lab certified, who knew about the risk of testing, when to not test and knew when to terminate during CPET, supervised the testing (10). Also, a medical responsible doctor was available at testing. Accuracy was emphasized through following lab procedures and calibration, ensuring as much accuracy of testing as possible.

Adolescents had to use time on this project and travel back and forth from training and testing facilities. However, there were benefits of participating in this study, such as the possibility of improving cardiorespiratory fitness, chances to make friends with the other participants and being in part of a group, especially with others with the same disease. Knowledge from the present study could also be of benefit for other adolescents with asthma and for knowing better how to plan an RCT later.

The main study got financial support from the Norwegian Association of Asthma and Allergy (NAAF) to pay the instructors, but master students did not receive any funding.

Being open about the results no matter if they are significant or not is important ethically. Not presenting them as improvement or changes when the p-values were above the chosen significance level, have been an important decision. This is because we cannot know whether

the results occurred by chance or because of the intervention. Changes in “wrong” directions or no changes at all can be as important findings as changes in “right” directions.

There was taking considerations to protects revealing the identity of adolescents with asthma participating in the study. The expression “from two study sites in Southern Norway” in the and article was a conscious choice, making it harder to guess who the participating adolescents with asthma were. Individual changes, as shown in figure 1 and 2 in the article are presented without ID, to ensure confidentiality for adolescents with asthma participating in the study.

4.6 Future research

Additional work to better understand the ventilatory mechanism in adolescents is needed. The effect of exercise at VO_{2peak} has on BR and EFL should be investigated in randomized controlled trials. The changes of BR and EFL at VO_{2peak} should be considered along with dyspnea index, VE/VCO_2, EELV, EILV, and VE_{peak} to better understand how BR and EFL at VO_{2peak} change due to an exercise intervention. Also, changes at submaximal exertion could be of interest as well as with VO_{2peak}, since exercise is often done at submaximal exertion. Assessing EFL through comparing the extFVL within MVFL should be used, for better visualization of a potential EFL during exercise and the extent of EFL (20). However, the extFVL/MFVL-analysis should be further examined for reliability and validity (20).

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Part 2: Changes in breathing reserve and expiratory flow limitation at peak exercise intensity after a 10-week exercise intervention in adolescents with asthma

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ABSTRACT

Introduction The aim of this study was to assess changes in breathing reserve (BR) and expiratory flow limitation (EFL) at peak oxygen uptake (VO_2peak) after an exercise intervention in adolescents with asthma.

Methods Fifteen adolescents with asthma, aged 13-18 years, participated in one-hour of exercise two times a week for ten weeks. Data collection included pre- and post-testing with spirometry at rest and EFL and BR at VO_{2peak} were examined when adolescents performed cardiopulmonary exercise tests (CPET) with intrabreath (IB)-maneuvers. Wilcoxon Signed Rank Test was used to determine the significance of the change in variables before and after the intervention, while Spearman's rho was used to assess correlation at post-assessment. Values are measured at VO_{2peak} and are presented as median with interquartile range unless otherwise stated.

Results Compared to baseline, EFL remained unchanged from (0.0 [23]) to (0.0 [0.0]). BR was before the exercise intervention (-0.6 % [15.6]) and (0.5 % [13.2]) after the exercise intervention. VO_{2peak} was before the exercise intervention (39 ml/kg/min [16.2]) and (42.6 ml/kg/min [19.5]) at post-assessment. There was a negative correlation of ρ= -0.4 between BR and VO_{2peak}.VO_{2peak} showed also a negative correlation of ρ= -0.4 with EFL. Minute volume (VE) showed a correlation of ρ=0.1 with EFL while BR and VE_{peak} had a correlation of ρ= 0.3). All correlation variables checked were at post-assessment and non-significant.

Conclusion BR remains low and there is no change or findings of EFL after a 10-week exercise intervention, in adolescents with asthma at VO_{2peak}, compared with the baseline assessment

Key messages

- This study aims to describe changes in ventilatory limitation among adolescents with asthma participating in an exercise intervention.
- Breathing reserve was low both before and after the exercise intervention for adolescents with asthma. No expiratory flow limitation was found before or after the exercise intervention for adolescents with asthma.

Abbreviations: EFL: Expiratory flow limitation **BHR**: Bronchial hyperresponsiveness

EIB: Exercise-induced bronchoconstriction **BR:** Breathing reserve **PA**: Physical Activity **HR_{max}:** Maximum heart frequency **CPET:** Cardiopulmonary exercise test **VE:** Minute ventilation **MVV**: Maximal voluntary ventilation **EELV:** end-expiratory lung volume **FEV_1:** forced expiratory volume in 1 second **BF**: breathing frequency **VC:** vital capacity **VE**: minute ventilation: **VO_2:** oxygen uptake **$VO_{2\text{-}peak}$:** Highest VO_2 achieved on a test performed to limit of tolerance **VT**: tidal volume **EILV:** End inspiratory lung volume, **extFVL:** tidal exercise flow-volume loop **MFVL:** maximal flow-volume loop **IC:** inspiratory capacity **ATS**: American Thoracic Society **ICON**: International consensus on pediatric asthma **PA**: Physical Activity

INTRODUCTION

According to the international consensus on pediatric asthma (ICON), asthma can be defined as

> […]A chronic inflammatory disorder associated with variable airflow obstruction and bronchial hyperresponsiveness (BHR). It presents with recurrent episodes of wheeze, cough, shortness of breath and chest tightness. [1]

The worldwide burden of asthma continues to rise.[2] Asthma is considered one of the most common chronic diseases in children.[1]Bronchial obstruction triggered by intensive physical activity (PA), exercise-induced bronchoconstriction (EIB), is not unusual for adolescents with asthma.[3] Asthma can limit the participation of PA for adolescents, for avoiding EIB and dyspnea in exercise.[4] Dyspnea is regarded as the subjective perception of breathless, but whether this represents expiratory flow limitation (EFL) remains unexplained to this date.[5] EFL is defined as the percent of tidal expiratory flow (extFVL) that meets or exceed the maximal flow volume loop (MFVL).[6] This means, how much of the ventilatory output that closely approaches or meets the ventilatory capacity (VC).[5] There are a few studies that examined EFL in children without asthma.[7,8.] In children without asthma, one will expect that children will have EFL during exercise, due to different regulation in children than in adults.[7] In the study by Nourry et al. 2006, EFL was examined in eighteen pre prepubescent children without asthma during maximal exercise, whereas ten of the eighteen children had EFL at maximal exercise.[7] However, in adolescents with asthma, few studies have examined EFL at VO_{2peak}.

Reduced breathing reserve (BR), <15%, at peak oxygen uptake (VO_{2peak}), can also indicate a ventilatory limitation in adolescents. [9,10] BR is the difference between measured maximal voluntary ventilation (MVV) and the ventilation (VE) measured at VO_{2peak}.[6] At VO_{2peak}, one would expect that adolescents without asthma, have around 20-40% BR.[9] However, it is not uncommon for adolescents with increased VO_{2peak} to have a low BR if they use all of their ventilatory capacity (VC).[9,10] To our knowledge, it is not known whether BR in adolescents with asthma can be changed after an exercise intervention.

The aim of this article is to describe how BR and EFL at VO_{2peak} change after a 10-week exercise intervention, compared with baseline assessment before the intervention.

METHODS

Design

The present study was a subproject of Physical Activity and Asthma in Youth (PLAY) study, an exercise intervention study with a pre-post single group design. The comparisons are made within this group and no control group was included, making this study a within-group design.[ref]

Exercise intervention

The study was conducted at two study sites in southern Norway at winter/spring and autumn/winter months apart from pollen season. The intervention period was over ten weeks, two times a week, one hour each time and located indoors. The activities were taken from an activity bank developed by bachelor students in sport from the University of Agder and were adjusted with what motivated the participants. The exercise was a combination of group-based activities indoors and outdoors based on relays, obstacle courses, and circuit training, and activities were adjusted so they were easy to complete in relation to gross motor and coordination skills. The exercise intervention was lead by two experienced sports instructors from two study sites. One of the two was present to organize activities, while the other participated in the session along with the adolescents.

The adolescents wore a heart rate (HR) monitor (Polar M400, Polar Electro OY, Kempele, Finland) during all sessions for the recording of exercise intensity. The HR data from each

session was registered and transferred to a computer at the lab and was exported into excel, and then calculated.

To be included in the study, participants had to be between 13 and 18 years of age. Symptoms of dyspnea, tightness in the chest and/or wheezing in the chest had to be experienced during the last 12 months, or use of asthma medications during the last months. A pulmonologist, allerlogist or pediatrician had to confirm the asthma diagnosis. In addition, participants had to be living within a one-hour traveling distance from the training facilities. Exclusion criteria included comorbidities such as upper airway infection the last week before pre-test, movement problems, heart disease, cancer and diabetes type 1 and/or travel distance above one hour from training facilities. Participants were recruited through the list of the allerlogist, which could confirm that their participation was medically safe and that participants met the inclusion criteria. Participants and their parents were informed about the potential burden with participation.

Measurement of height, weight, and body mass index

Height and weight were measured by a stadiometer (Seca 713, Birmingham, UK) to the nearest 0,5 cm and 0,1 kg in daily clothes without shoes. Body mass index (BMI) was calculated as body mass (kg) divided by height (m)squared and defined with standard deviation scores (z-scores) with international limits for BMI adjusted for age and sex according to Cole et al.[11]

Measurement of intensity during the intervention

For the recording of exercise intensity during the exercise intervention, participants wore a heart rate (HR) monitor (Polar M400, Polar Electro OY, Kempele, Finland). The HR data from each session was registered and transferred to a computer at the lab and was exported into excel, for further calculation of HR data.

Measurement of lung volumes and flow limitation

Before CPET, gas calibration was done. When calibrating gas analyzer, known gas concentrations that spanned the range of expected measurements were used. The chosen exercise protocol for CPET was a modification of Balke.[12] For CPET, the mask was adjusted

and placed on the participant's nose and mouth and connected to an oxygen analyzer ((OxyconPro, Jaeger, Würtzburg, Tyskland). Breath by breath method was used. This method analyzes the volume and gas of every expiratory breath.[10] Participants ran on a treadmill (Woodway, ELG 90/200 Sport, Weil Am Rhein, Germany) with increasing speed and incline every second minute after a warm-up of 4 percents inclines and 4,0 km/h during the first three minutes. Participants were encouraged to run to exhaustion. VO_2 was measured at peak exercise intensity at CPET to determine $VO_{2peak.}$VE, EELV, EILV, and VE/VCO_2 ratio was measured at VO_{2peak} during CPET. Intrabreath measurements were used for assessment of expiratory flow limitation (EFL) during exercise. During the CPET extFVL was recorded using intrabreath (IB) maneuver so that extFVL could be placed within the MFVL obtained from the spirometry performed at rest before the CPET.[6] If possible, the second last extFVLrecorded before the IB maneuver was used for analysis. If not possible to use the second last extFVL due to low quality, such as irregular loop or no recording, the last loop before the IB maneuver was used. The second loop after a full IB maneuver was used a third choice as long as there we no signs of driftings before and after the IB maneuver or within the first extFVL recordings.[6] If there was not possible to obtain a tidal loop without drift, recordings were set to missing, and therefore no measure of EELV, EILV or EFL could not be given for that specific time point. Researchers conducted manual control of each IB recording. Only recordings with a rapid inspiration followed by a comparable expiration and a similar extFVL as before the maneuver were accepted. The percentage of the extFVL that meets or exceeds the MFVL, indicated the presence and degree of EFL.[6] Data were analyzed with the software program SentrySuite 2.21, CareFusion, Hoechberg, Germany. The CPET was only done by research members with lab competence and certification. The extent of EFL was defined were extFVL meets or exceeded the MFVL from rest according to Johnson. [6]

Measurement of lung function

Before spirometry, a 3-liter calibration syringe was used to calibrate the flow sensor. During spirometry testing, the adolescents were seated on a chair and given a nose clip. Lung function was assessed with MasterScreen Pneumo spirometer (CareFusion, Würzburg, Germany). For each adolescent, three measurements of FVC and FEV_1 The best FVC and FEV_1 measurements were kept for determining the greatest MFVL loop along with the extFVL[6]. Ethnicity, gender, height, weight, and age were plotted into the computer along for adjusting the spirometric values according to the recommendation of the American Thoracic

Society (ATS).[10] The expected spirometry values were registered as a percentage with reference values according to Quanjer et al.[14]

Measurement of maximal voluntary ventilation and breathing reserve

For calculating BR, MVV was estimated by multiplying FEV_1 with 35, as this method correlates with MVV.[ref] FEV_1 was measured in a Master Screen spirometer (CareFusion, Würzburg, Germany), and thereafter multiplied with 35. VE at VO_{2peak} during CPET was then divided by the estimated MVV through FEV_1 x 35[13,15]. This gave the used percentage of BR. For calculating the remaining BR to, this value was then subtracted by 100.

Measuring asthma control

Asthma control questionnaire (ACQ) was used to determine how well-controlled asthma the adolescents had.[16] ACQ was measured at baseline and after the intervention. Participants answered the questionnaire on question 1 to 6. The last question, 7, was filled out by test leader based on FEV_1 before CPET. A score <1.0 will have adequately controlled asthma.[16] Scores >1.0 will be viewed as not well-controlled asthma.[16]

Calculation of dyspnea index

Dyspnea index at VO_{2peak} was calculated by dividing VE at VO_{2peak} with the estimated MVV, using FEV_1 multiplied 35.[17]

Statistical analysis

Statistic analysis was run by the Statistical Program for Social Services (SPSS), version 25, (SPSS Inc., Chicago, USA). SPSS for Windows was used. P-values <0.05 was considered statistically significant. Due to skewed data and low sample size non-parametric test was done. Variables before and after the exercise program were compared using the Wilcoxon signed rank test. Correlation of the characteristics was checked with Spearman's rho (ρ).

RESULTS

Baseline findings

Table 1 compares the subject characteristic at baseline in the adolescents who completed and in the adolescents who dropped out of the study. In total, six adolescents with asthma from

two study sites in southern Norway dropped out of the study, three adolescents with asthma from each of the two study sites. The main reason for drop-out was long travel distance, injury and/or that they were occupied with school. Two adolescents with asthma dropped out before the intervention started, while the four dropped during the intervention. As seen in table 1, adolescents with asthma who dropped out were slightly younger the participants who completed the intervention. In addition, the BMI z-score was higher for the group of adolescents with asthma who dropped out (1.5 [1.3]) than the group of adolescents with asthma which completed 0.5 (1.1) Predicted values of FEV_1 (%) were lower 90.2 (13) in adolescents who completed than those who dropped out (100.5 [23.5]). The ACQ score at baseline was 0.9 (0.9) for the adolescents who completed and 0.9 (0.7) for the adolescents who dropped out, meaning adequate asthma control in both groups.[16] Adolescents who completed the study had lower VO_{2peak} (39.0 ml/kg/min (16.2) at baseline than the adolescents who dropped out 45.9 ml/kg/min (14.6). Among those who completed, there were more male (*n*=9) than female adolescents (*n*=6) participating in the exercise intervention.

Table 1 Subject characteristics at baseline in adolescents asthma (*n*=15) who completed and adolescents with asthma who dropped out of the study (*n*=6). Numbers are given as median with interquartile range (IQR) unless otherwise stated.

Variables	Adolescents who completed the intervention *(n*=15)	Adolescents who dropped out of the intervention (*n*=6)
Male, n (%)	9 (60%)	3 (50%)
Age (yrs)	16.3 (1.4)	15.2(2.1)
Height (cm)	173.5 (10.0)	172 (16.8)
Weight (kg)	65.2 (12.5)	73.5 (16.4)
BMI z-score	0.5 (1.1)	1.5 (1.3)
*FEV_1** (% of predicted)	90.2 (13)	100.5 (23.5)
*FVC** (% of predicted)	90.6 (16.9)	100 (20.3)
FEV_1/FVC-ratio* (%)	90% (10)	90%(0)
ACQ	0.9 (0.9)	0.9 (0.7)
VO_{2peak} (l/kg/min)	39 (16.2)	45.9 (14.6)

*Before asthma medication. *FVC:* Forced vital capacity, *FEV_1:* Forced vital capacity during the first second, *VO_{2peak}:* peak oxygen uptake, *MVV:* Maximum voluntary ventilation, *VE_{peak}:* Peak minute ventilation *ACQ*: Asthma control questionnaire *BMI-z-score:* Body Mass Index standard deviation score

Attendance rate and heart rate

The attendance rate during the exercise intervention was 80%. Mean heart rate (HR) during sessions were 151±10 and mean total minutes ≥80% of maximal HR (HR_{max}) were 292±172 and ≥90% of HR_{max} was 144±129.

Change in breathing reserve and expiratory flow limitation

Mostly, no EFL was seen both before and after the intervention in the group, from 0.0 % (23) to 0.0 % (0.0) Figure 1 illustrates the individual change of EFL in the adolescents at post-assessment. Ten adolescents with asthma had no EFL both before and after the exercise intervention, which can make it hard to notice adolescent with no EFL in figure 1. Four adolescents had a decrease in EFL while one adolescent had an increase in EFL.

Table 2 shows characteristics in adolescents with asthma, comparing before and after the exercise intervention. As figure 2 shows, the adolescent with asthma had different individual changes in BR at VO_{2peak} at post-assessment. Approximately half of the adolescents increased their BR while the other half of adolescents decreased their BR at post-assessment. Before the exercise intervention, the BR was -0.6% (15.6) while BR was -0.5% (13.2) at post-assessment, as seen in table 2.

Table 3 shows the correlation between the variables. There was a negative correlation between the variables BR and VO_{2peak} (ρ=-0.4), EFL and VO_{2peak} (ρ=-0.4) Also, a positive correlation between VE and VO_{2peak} (ρ=0.1) and a positive correlation between EFL and BR (ρ=0.3) was seen. All correlation variables were at checked at post-assessment and were non-significant.

Table 2 Cardiorespiratory variables and ventilatory changes of adolescents with asthma, before and after 10 weeks of exercise intervention (*n*=15)

Characteristic	Before	After	p-value
V0$_2$peak (l/kg/min)	39.0 (16.15)	42.6 (19.5)	0.3
BR at VO$_{2peak}$	-0.6 (15.6)	0.5 (13.2)	0.6
EFL (%)	0.0 (23.0)	0.0 (0.0)	0.3
VEpeak (l/min)	111.8(37.0)	117.5(61.0)	0.4
EELV (l/min)	1.1 (1.1)	1.1 (1.1)	0.6
EILV (l/min)	3.1 (1.6)	3.1 (1.4)	0.6
VE/VCO$_2$	34.2 (6.2)	33.8 (7.6)	0.03

Data are presented as median. All variables are at peak oxygen uptake (VO_{2peak}) Significance was checked with Wilcoxon (IQR). *BR:* Breathing reserve, *V0$_{2peak}$:* Peak oxygen uptake, *VE:* Minute ventilation *EELV: End-expiratory volume, EILV:* End-inspiratory volume *VE/VCO$_2$:* Ventilatory equivalent of carbon dioxide to the minute volume

Change is cardiorespiratory fitness

$VO_{2peak,}$ as shown in table 1, were 39.0 ml/kg/min (16.5) at baseline and 42.6 ml/kg/min (19.5) at post-assessment. VE/VCO_2 decreased significantly from 33.4% (5.7) to 33.1% (7.1) (*p*=0.02). VE_{peak} was 111.8 l/min (37) at baseline and 117 l/min (61) at post-assessment.

Table 3 Spearman's correlations with significance value between main variables at post-assessment after 10-weeks of exercise intervention in adolescents with asthma

Correlation variables checked	Significance *(p)*	Spearmans'rho coefficient(ρ)
BR and VO_{2peak}	0.8	-0.4
EFL and VO_{2peak}	0.1	-0.4
EFL and VE_{peak}	0.4	0.1
BR and VE_{peak}	0.3	0.3

All variables are measured at peak oxygen uptake *($VO2_{peak}$)BR*: Breathing reserve, *EFL*: Expiratory flow limitation, VE_{peak}: Peak minute volume

DISCUSSION

Mostly, no EFL before and after the exercise intervention was found in the adolescents (figure 1). However, four adolescents had a reduced EFL at post-assessment, compared with baseline (figure 1). Asthma is a heterogeneous disease,[18] therefore, the exercise intervention could have influenced the adolescents differently. Although no significant change in the group, figure 1 shows a great improvement in these four adolescents. Reduced EFL in these four adolescents could be due to improved medication or improved asthma control along with exercise since several of the adolescents used their medication more often at the end of the intervention. In ten adolescents, there was no EFL at post-assessment which can indicate that exercising at VO_{2peak} possibly not triggers BHR in adolescents with asthma. Improved asthma control, mild asthma or improved medical treatment of asthma could also be influencing why the adolescents mainly in the group had no EFL. According to Philpott, Hougton and Luke, adolescents are able to participate in any physical activity if symptoms are well-controlled [19] Results could possibly have been different if the adolescents had severe asthma. Reasons for finding no change in EFL could be type two error due to low sample size.[20] Most adolescents had no EFL at baseline, which can make it harder finding a significant decrease of EFL at the post-assessment. Results could possibly have been different if there were some degree of EFL, to begin with.

In the group of adolescents as shown in table 2, approximately no BR was left at post-assessment indicating that the adolescents either still is ventilatory restricted, or that that they still use all their VC.[9] Nonetheless, incorrect measurement or estimate of MVV could have been influencing these results. Low sample size and a, therefore, a higher probability for type two error could be reasons for this change.[20] Half of the group of adolescents, had a decrease of BR, as illustrated in figure 2. The decrease of BR in adolescents could also signalize ventilatory limitation or that the adolescents improved their capability of using more of their VC.[9] The rest of the adolescents had an increase of BR, but still under expected values at post-asssment.[9,10]The increase of BR in some adolescents could mean that these adolescents have a larger potential to use of their VC, or that they are not ventilatory restricted to exercise. However, these were still below expected values. [9,10] As one can notice in figure 2, some BR values were below zero at post-assessment. If FEV_1 were not done properly (such as not doing their best effort) or dilation of lungs in exercise can be reasons for the negative values of BR.[21]

As seen in table 3, VO_{2peak} had a small negative correlation with BR, which could indicate that with increasing VO_{2peak}, BR would possibly decrease. Also, no change of VE_{peak} was seen which could have influenced why the adolescents with asthma had no EFL. It is suggested that with a decrease of VE_{peak}, this will decrease BHR. [2,17]

There was a small, negative correlation of EFL and $VO_{2peak,}$ which possibly could indicate that if VO_{2peak} is increased, EFL will decrease. However, the significance of the correlation between EFL and VO_{2peak} was low, as seen in table 3. This implies that if we measured the same variables on another group of adolescents with asthma, we would possibly not get the same correlation. When *n* is small it is possible a high correlation coefficient can occur by chance.[22] The correlation between EFL and VO_{2peak} does not mean that the change in one of the variables will necessarily produce a corresponding change in the other; for example, when there is no EFL in the adolescents, and EFL is negatively correlated with VO_{2peak}.

The dyspnea index did not change, nor was it elevated. According to Hallstrand, Bates and Schoene, the dyspnea index is elevated in adults with EFL.[17]Since the dyspnea index not were elevated in our study, this supports the findings of no EFL in most adolescents with asthma in this study. The significant decrease of the ventilatory equivalent of VCO_2 (VE/VCO_2) can also indicate improvement of anaerobic threshold, ventilatory efficiency and therefore improved cardiorespiratory fitness.[13] ATS states as well that the ratio of VE/VCO_2 should be

<36 at VO_{2peak} and a higher value (>36) represents the presence of airway resistance.[13] However, one would expect that with the significant decrease of VE/VCO_2, significant improvement in VO_{2peak} at post-assessment was seen along. Significant improvement in VO_{2peak} was not seen in our group of adolescents. Possible reasons for these findings could be that some of the adolescents had to stop the test before completely reaching full exhaustion. No significant improvement of VO_{2peak} at post-assessment could also be a consequence of type two error.[20]

In the present study, there was no change in EILV or EELV. An increase in EELV is associated with EFL and a breathing strategy with extra work of breathing (WOB) due to reduced inspiratory muscle endurance.[6]As EELV increases so does the degree of EFL. [6] When exercise intensity increases, EILV should increase.[6] Failure to increase EILV as exercise intensity increases are related to a breathing strategy with an increased BF which can further increase EFL.[6] The adolescents had no change of either EELV or EILV which could have played a part in why there was no EFL in adolescents at post-assessment.

ExtFVL/MFVL-analysis used in the present study has been an advantage this study in terms of visualization of degrees of EFL.[6] However, extFVL/MFVL-analysis is not yet a well-established method and there a few studies to compare these results with. Time prior to practicing IB maneuver should be taken regarding the correct placement of extFVL within MFVL.[6]Also, consideration in the method for calculation in BR should be is important. Use of FEV_1 multiplied with 35 is also easier to calculate through the CPET testing.[15]However, FEV_1 does not always pick up the change in the improvement of MVV in some individuals, as noted by Hallstrand, Bates and Schoene.[17]

The study has limitations due to low sample size. Also, the single pre-post design is considered a weak research design since there is no random allocation of participants.[20] Hence, further research of changes in EFL and BR in adolescents with asthma is required. Almost all adolescents either remained at no EFL or decreased their EFL at $VO_{2peak,}$ which could indicate that EFL and BR in adolescents with asthma and exercise are safe to assessing further in a randomized controlled trial with more participants, along with proper medication.

In conclusion, the present study shows that BR remains low and there is no change and findings of EFL after a 10-week exercise intervention, in adolescents with asthma at VO_{2peak}, compared with the baseline assessment.

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Contributors AN conceived the research question, collected data, performed the data analysis, interpretation of findings and wrote the manuscript. TW, JS, and TS contributed to the study design. TW and JS contributed to data analysis and interpretation of findings and critically reviewed the manuscript. KRT, TS contributed along with AN with the collection of data. TW and TS were responsible for all data collected and provided access to the data. AN was granted full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis. NAAF did not play a role in the design, analysis or interpretation of results.

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Competing interests: None declared

Patient consent for publication Not required.

Ethics approval The regional ethical committee approved this study

Data sharing No additional data are available due to privacy and confidentiality laws.

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Appendix 1: Figures for article:

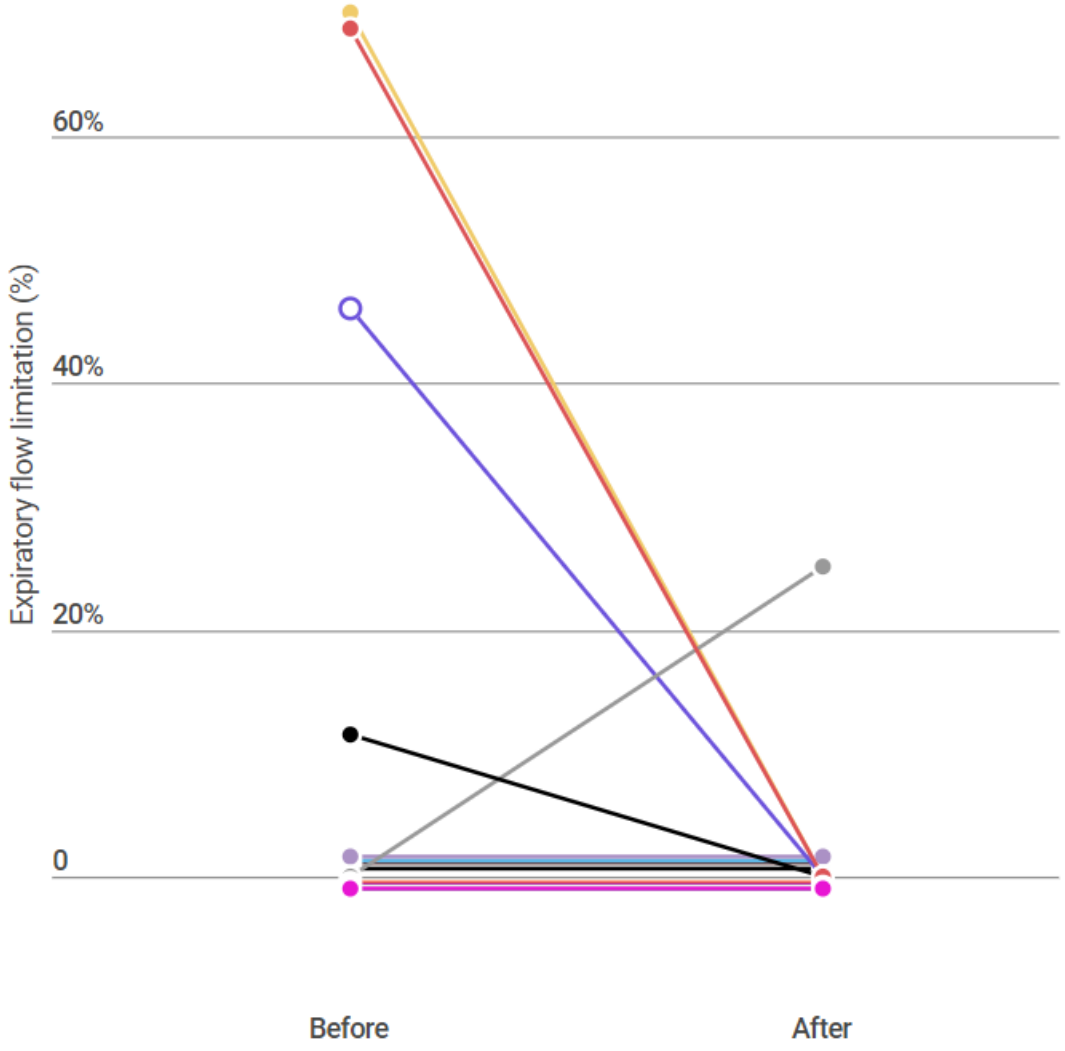

Figure 1. Expiratory flow limitation before and after 10 weeks of exercise intervention with adolescents with asthma (*n*=15).

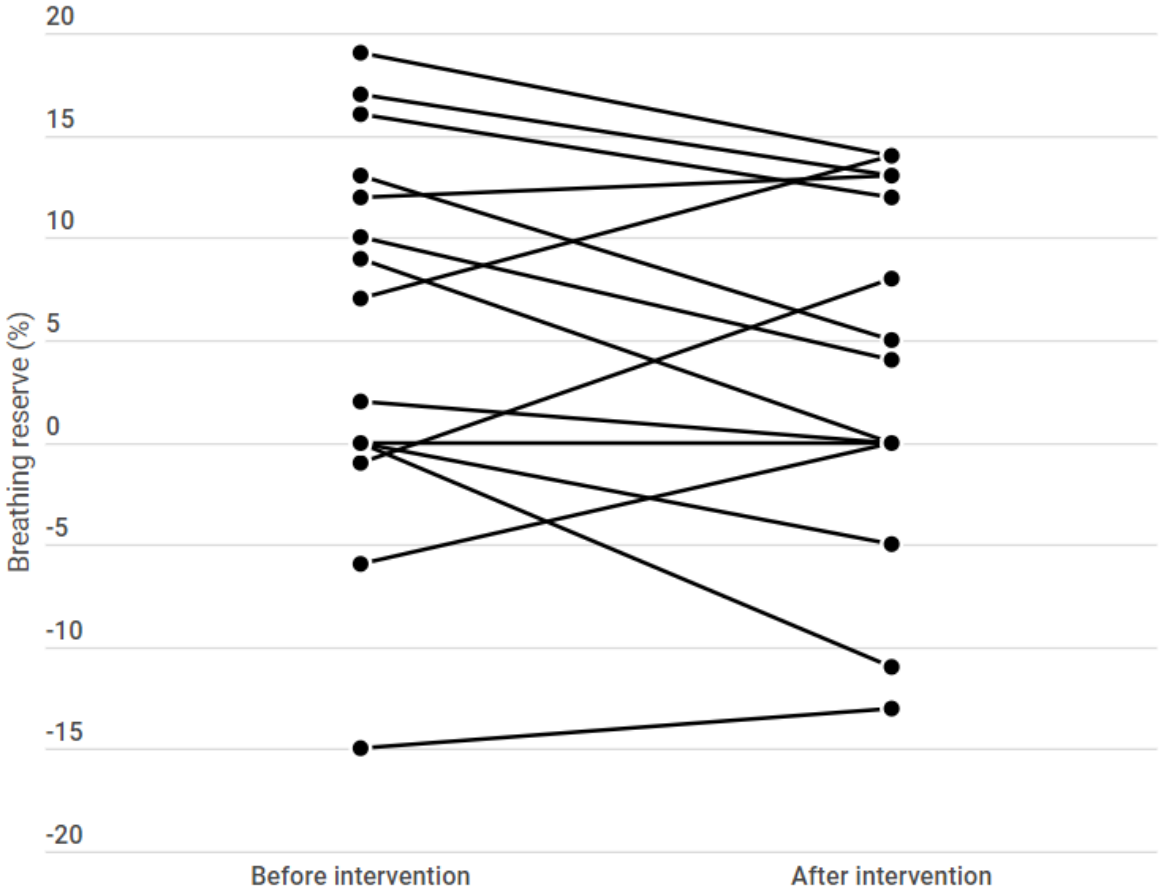

Figure 2. Breathing reserve (%) before and after 10 weeks of exercise intervention in adolescents with asthma. (*n*=15)

Part 3 Appendices for the master thesis

Appendix 1: List of abbreviations

Abbreviations

EFL: Expiratory flow limitation

BR: Breathing reserve

PA: Physical activity

BHR: Bronchial hyperresponsiveness

EIB: Exercise-induced bronchoconstriction

extFVL: tidal exercise flow-volume loop

MFVL: maximal flow-volume loop

CPET: Cardiopulmonary exercise test

VE: Minute ventilation

MVV: Maximal voluntary ventilation

FEV_1: Forced expiratory volume in 1 second

FVC: Forced vital capacity

BF: Breathing frequency

VC: vital capacity

VE: minute ventilation

VO_2: oxygen uptake

$VO_{2\text{-peak}}$: Highest VO_2 achieved on a test performed to limit tolerance

VT: tidal volume

EILV: End- inspiratory lung volume

EELV: End-expiratory lung volume

IC: inspiratory capacity

ATS: American Thoracic Society

ICON: International consensus on Pediatric Asthma

Appendix 2a: Information letter of consent and consent form, for parents:

UNIVERSITETET I AGDER

NIH NORGES IDRETTSHØGSKOLE

Forespørsel om deltakelse i forskningsprosjektet

PLAY (PhysicaL activity and Asthma in Youth)

Fysisk aktivitet er viktig for alle unge med astma, blant annet fordi god fysisk form er med på å kontrollere sykdommen og gi god helse. Hva som skal til for at ungdom med astma positivt mestrer en frisk og fysisk aktiv hverdag, vet man derimot for lite om.
Dette er derfor et spørsmål til deg om å la din ungdom delta i en forskningsstudie for å undersøke hvordan vi kan hjelpe unge med astma til en friskere og mer aktiv hverdag. Vi ønsker å finne ut hvordan vi i fremtiden kan gi bedre behandling til barn og unge med astma. Norges Idrettshøgskole (NIH) og Fakultet for helse- og idrettsvitenskap ved Universitetet i Agder (UiA) og er sammen ansvarlig for studien som gjennomføres i samarbeid med helsetjenesten på sykehus og i kommunen. Leder av prosjektet ved NIH er Førsteamanuensis Trine Stensrud.

Hva innebærer PROSJEKTET?

En lege med spesialisering i astma og allergi vil være medisinsk ansvarlig for studien.

Ungdommen din skal først gjennomgå en kondisjonstest. Denne testen utføres på Arbeidsfysiologisk testlab på NIH, første gang i løpet av november/desember. Testen går ut på at ungdommen skal gå og løpe i til sammen 15-20 minutter på en tredemølle, samtidig som det puster gjennom en maske. Mot slutten av testen vil ungdommen bli ordentlig sliten. Vi måler da hans/hennes maksimale oksygenopptak, som er et mål på kondisjon. I forbindelse med løpetesten vil vi også ta en liten blodprøve fra fingeren til din ungdom, og han/hun vil kjenne et lite stikk som kan være vondt, men raskt går over. Vi vil også før løps-testen måle lungefunksjon slik som dere er vant til fra legen og/eller sykehuset. I forbindelse med testen vil ungdommen også fylle ut et spørreskjema. Hele besøket på testlabben tar ca en time.

Ungdommen får også utlevert en måler som skal bæres rundt overarmen i 7 sammenhengende dager. Denne registrerer ungdommens daglige energiforbruk. Ungdommen vil gjennomgå kondisjonstesten på nytt og ha måleapparatet på i 7 dager, etter de første seks ukene og helt til slutt i studien. Deretter vil alle ungdommene delta i en aktivitetsgruppe på 15-20 ungdommer to ganger i uken tirsdag og torsdag kl. 18-19 over en periode på ti uker. Aktivitetsøktene vil bli ledet av forskere og studenter ved Norges Idrettshøgskole. Fokuset er at ungdommene skal ha det gøy når de er i aktivitet. Øktene vil være lystbetonte og lekpreget, men likevel ha en høy intensitet. Øktene vil foregå innendørs på Norges Idrettshøgskole.

En forsker vil være tilstede og observere testing og aktivitet, og vil også intervjue din ungdom sammen med andre barn i grupper på inntil seks ved tre anledninger. Samtalene finner ikke

sted i gymsalen. Disse samtalene vil bli tatt opp på bånd, og forskeren vil gjøre notater fra sine observasjoner.

I prosjektet vil vi innhente og registrere opplysninger fra din ungdoms journal vedrørende astmasykdommen, symptomer og medisinsk behandling for å kartlegge grunnlaget for din ungdoms astmadiagnose.

Mulige fordeler og ulemper

Det utbetales ingen honorar for å være med i studien, og tilbudet er gratis.
Gjennom studien vil ungdommen få muligheten til å være i aktivitet sammen med andre ungdommer med astma, og forbedre sin fysiske kondisjon gjennom lystbetonte aktiviteter. Fysisk aktivitet kan også trigge ubehagelige symptomer og tett pust. Derfor vil vi at din ungdom gjennom hele prosjektet skal bruke sine medisiner som legen har foreskrevet, og den lege som er medisinsk ansvarlig vil også være tilgjengelig for råd og veiledning ved behov. Intervjuene som gjennomføres vil også åpne for refleksjon om egen situasjon og egen helse. Samtidig kan slike samtaler bli personlige. Det er derfor viktig at din ungdom selv er bevisst på hva hun/han deler og ikke. Du og din ungdom vil også bruke tid på å være med i studien. I tillegg til de to ukentlige øktene over tolv uker vil dere bruke opptil en time i forbindelse med tester før og etter studien, og opp til en time til intervju ved tre tilfeller i løpet av perioden. Intervjuene vil bli samordnet med øktene og/eller testingen.

Frivillig deltakelse og mulighet for å trekke sitt samtykke

Det er frivillig å delta i studien. Du eller din ungdom kan når som helst og uten å oppgi noen grunn trekke deres samtykke til å delta i studien. Dette vil ikke få konsekvenser for videre behandling eller oppfølging hos lege eller ved sykehuset. Dersom du ønsker at din ungdom skal delta, undertegner du og din ungdom samtykkeerklæringen på siste side. Om du nå sier ja til at din ungdom kan delta, kan du senere ombestemme deg og trekke tilbake ditt samtykke uten at det påvirker din eller din ungdoms øvrige behandling. Hvis din ungdom underveis velger å trekke seg fra aktivitetsopplegget men likevel opprettholder sitt samtykke til å være med på intervjuene er det tilrettelagt for det. Dersom du eller din ungdom senere ønsker å trekke dere eller har spørsmål til studien, kan dere kontakte Trine Stensrud, tlf 23262346 (e-post: trine.stensrud@nih.no) eller Julie Stang, tlf 23262244 (e-post: julie.stang@nih.no), ved Norges Idrettshøgskole.

Hva skjer med informasjonen om deg?

Testresultatene og informasjonen som registreres skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter din ungdoms opplysninger til en navneliste. Samtalene som blir tatt opp på bånd, vil bli skrevet ut som en tekst, og i den forbindelse samt i notater vil alle navn bli byttet ut. Det vil ikke være mulig å gjenkjenne ungdommen ved navn eller stemme uten og direkte høre på båndopptaket.

Det er kun autorisert personell knyttet til prosjektet som har adgang til båndopptaket, eller til navnelisten, og som kan finne tilbake til din ungdom.

Det vil ikke være mulig for utenforstående å identifisere din ungdom i resultatene av studien når disse publiseres. Opptak og andre opplysninger som kan knyttes til ditt barn vil slettes senest 31.12.2022.

Forsikring

Norges Idrettshøgskole er en statlig institusjon og er således selvassurandør.

Godkjenning

Prosjektet er godkjent av Regional komite for medisinsk og helsefaglig forskningsetikk, saksnr. hos REK (2017/1320).

Samtykke til deltakelse i PROSJEKTET

Jeg er villig til å delta i prosjektet

Sted og dato	Deltakers signatur
	Deltakers navn med trykte bokstaver

Som foresatte til_ (Fullt navn) samtykker vi til at hun/han kan delta i prosjektet

Sted og dato	Foresattes signatur
	Foresattes navn med trykte bokstaver

Sted og dato	Foresattes signatur
	Foresattes navn med trykte bokstaver

Jeg bekrefter å ha gitt informasjon om prosjektet

Sted og dato	Signatur
	Rolle i prosjektet

Appendix 2B, information letter and consent form, version for participants

UNIVERSITETET I AGDER

NIH NORGES IDRETTSHØGSKOLE

Forespørsel om deltakelse i forskningsprosjektet

PLAY (PhysicaL activity and Asthma in Youth)

Hvorfor gjør vi dette?

Dette er et spørsmål til deg som har astma om å delta i en undersøkelse om hva som kan tilrettelegge for en positiv deltakelse i fysisk aktivitet. Vi ønsker å finne ut hvordan vi kan hjelpe unge med astma til en friskere og mer aktiv hverdag. Fakultet for helse- og idrettsvitenskap ved Universitetet i Agder (UiA) og Norges Idrettshøgskole (NIH) er ansvarlig for prosjektet som gjennomføres i samarbeid med helsetjenesten i kommunen og på sykehus.

Hva innebærer studien?

Det første som skjer hvis du blir med er at du skal gjennomføre en test på Norges Idrettshøgskole på Sognsvann hvor du skal først gå, og så løpe på en tredemølle i til sammen ca. 15-20 minutter. På slutten av løpetesten blir du skikkelig sliten. I forbindelse med løpetesten vil vi også ta en liten blodprøve fra fingeren din, og du vil kjenne et lite stikk som kan være vondt, men raskt går over. Når du går og løper måler vi kondisjonen din ved at du puster gjennom en maske. Før du løper vil vi også måle lungefunksjonen din ved at du blåser det du kan i masken slik som du tidligere har gjort gjennom et munnstykke hos din lege eller på sykehuset. Videre vil du få utdelt en måler som du skal ha rundt den ene overarmen. Denne måler den daglige aktiviteten din, og du skal ha den på deg i 7 dager etter hverandre og gjøre det du pleier å gjøre. Før du går hjem fra testen skal du også fylle ut et spørreskjema.

Deretter skal du være med i en aktivitetsgruppe to ganger i uken i ti uker. Etter aktivitetsperiodene er slutt skal du gå og løpe på tredemølla og testes en gang til.

Aktivitetsgruppa du skal være med i vil bestå av 15-20 andre ungdommer på din alder, og aktiviteten vil foregå inne på Norges Idrettshøgskole på Sognsvann tirsdag og torsdag kl. 18-19.Aktivitetene vil være gøyale samtidig som du blir sliten. Aktivitetene blir ledet av trenere fra Norges Idrettshøgskole.

En forsker som ikke er trener vil være tilstede for å bli litt kjent med deg og aktivitetene du er med på. Han/hun vil også gjennomføres samtaler med deg og andre ungdommer i grupper på fem-seks ungdommer. Disse samtalene finner ikke sted i gymsalen. Det vil bli gjort lydopptak av disse samtalene.

Informasjon om din astma og din behandling fra din legejournal vil også bli innhentet i prosjektet.

Mulige fordeler og ulemper

Gjennom studien vil du få muligheten til å være i aktivitet sammen med andre ungdommer med astma, og forbedre din kondisjon gjennom gøy aktivitet. Fysisk aktivitet kan også trigge ubehagelige symptomer og tett pust. Derfor vil vi at du hele tiden skal bruke dine medisiner som din lege har foreskrevet, og en lege vil være tilgjengelig for råd og veiledning ved behov som medisinsk ansvarlig.

Samtalene med forskeren i grupper vil handle om din opplevelse av din hverdag med astma. Slike samtaler kan bli personlige. Det er derfor viktig at du selv bestemmer hva du vil fortelle til de andre og til forskeren.

Du vil bruke tid på å være med i studien. I tillegg til trening to kvelder i uken i tolvuker vil det ta omtrent en time når vi skal teste din kondisjon før og etter aktivitetsperioden. Hver gruppesamtale med forskeren vil vare i en time og vi skal ha tre samtaler i løpet av perioden. Samtalene vil være rett før eller etter en av treningene.

Hva skjer med det vi får vite om deg?

Det vi får vite om deg skal kun brukes for å finne ut hvordan vi kan hjelpe unge med astma til en friskere og mer aktiv hverdag. Alle opplysninger vi får vite om deg vil registreres med et kodenummer, ikke navn og fødselsnummer. I et låst arkivskap oppbevares informasjon om hvem som har hvilket kodenummer. I samtalene som blir tatt opp på bånd vil alle navn bli byttet ut når vi skriver ut samtalene som tekst. Det vil heller ikke være mulig å gjenkjenne din stemme uten og direkte høre på båndopptaket.

Det er kun forskere i prosjektet som har adgang til båndopptaket, den hemmelige koden og til navnelisten som kan finne tilbake til deg. Det vil ikke være mulig for andre enn forskerne å finne igjen deg i resultatene av studien når disse skal presenteres. Men alle som er med vil kanskje kunne huske å kjenne igjen ting hvis dere leser om det etterpå. Opptak og andre opplysninger som kan knyttes til deg vil slettes senest 31.12.2022.

Vil du være med?

Det er frivillig å være med. Om du ombestemmer deg og finner ut at du ikke har lyst å være med lenger, er det helt greit. Det vil ikke ha noe å si for din oppfølging på sykehuset, hos helsesøster eller din lege. Dersom du ønsker å delta, skriver du ditt navn på siste side i skjemaet som dine foreldre/foresatte har fått. Om du slutter på aktivitetene men vil være med på samtalene i gruppe kan du det. Hvis du har spørsmål til oss, kan du gjerne ringe eller sende e-post. Telefonnummer og e-post står nederst på arket.

Vennlig hilsen,

Anette Nielsen (Masterstudent) Kristine Ringsjø Tufte (Masterstudent)
Tlf 48033629 984 48 365

anette.nielsen@studmed.uio.no kr.tufte@hotmail.com

Seksjon for idrettsmedisinske fag
Norges Idrettshøgskole

Appendix 3: Regional ethical committee approval

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Mariann Glenna Davidsen	22845526	19.09.2017	2017/1320 REK sør-øst B
			Deres dato: 13.06.2017	Deres referanse:

Vår referanse må oppgis ved alle henvendelser

Sveinung Berntsen Stølevik
Universitetet i Agder

2017/1320 Fysisk aktivitet og astma hos ungdom

Forskningsansvarlig: Universitetet i Agder
Prosjektleder: Sveinung Berntsen Stølevik

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst) i møtet 23.08.2017. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10.

Prosjektleders prosjektbeskrivelse

«Hensikten med prosjektet er å utvikle, gjennomføre og evaluere to treningsintervensjoner med gruppetrening med høy intensitet og lekbetonte aktiviteter som er lette å mestre for ungdom med astma henholdsvis i alderen 13-16 år og 16-19 år, og å undersøke hvordan det endrer selvforståelse, motivasjon for trening, nivå av fysisk aktivitet, fysisk form, helserelatert livskvalitet, astmakontroll og ventilatorisk flowbegrensning under anstrengelse. Studien har et mixed-methods design som inkluderer klinisk testing av lungefunksjon og fysisk form, validerte instrumenter for motivasjon, livskvalitet og astmakontroll, registrering av treningsintensitet ved puls, objektiv fysisk aktivitet ved bruk av aktivitetsmonitor, og kvalitative data fra deltakere basert på fokusgruppeintervjuer og

feltobservasjoner av trening og testing. Basert også på registrering av aktiviteter, oppmøte og gjennomføring vil det bli lagt et kunnskapsgrunnlag for en randomisert kontrollert studie etter tilsvarende mønster»

Komiteens vurdering

Dette er en masteroppgave som har som formål å øke kunnskap om hvordan en treningsintervensjon, med tanke på ungdommer med astma, kan gjennomføres i ungdommenes lokalmiljø. Prosjektet vil også kunne bidra til å kartlegge endring av adferd, mestring og motivasjon spesifikt for denne pasientgruppen, samt hvordan dette kan påvirke aktivitetsnivå, sykdomsaktivitet og livskvalitet.

Ved inklusjon vil det bli gjennomgått journaler og/eller utført objektive tester for verifisering av astmadiagnosen hos samarbeidende fastleger, privatpraktiserende spesialister og sykehus, avhengig av hvor deltakerne rekrutteres fra. Det skal også innhentes nye helseopplysninger fra tester og undersøkelser i forbindelse med astma diagnosen; lungefunksjon, hjertefrekvens og laktet prøve av kapillær. Deltakerne skal i tillegg fylle ut spørreskjema om livskvalitet, utføre treningsøvelser og gjennomføre fokusgruppeintervju.

Det er lagt opp til at deltakerne skal møte to ganger per uke i 12 uker for gjennomføring av studien.

Alle tester og undersøkelser vil være i tråd med vanlig standard behandling.

Besøksadresse:
Gullhaugveien 1-3, 0484 Oslo

Telefon: 22845511
E-post: post@helseforskning.etikkom.no
Web: http://helseforskning.etikkom.no/

All post og e-post som inngår i saksbehandlingen, bes adressert til REK sør-øst og ikke til enkelte personer

Kindly address all mail and e-mails to the Regional Ethics Committee, REK sør-øst, not to individual staff

Samtykke/rekruttering

Samtykke vil bli innhentet fra foreldre til barn i alderen 13-15 år, og fra deltakerne selv i alderen 16-18 år.

Aktuelle deltakerne vil bli identifisert gjennom samarbeid med skolehelsetjenesten, fastleger, privatpraktiserende spesialister og offentlige sykehus. Samarbeidende instanser vil på vegne av prosjektet informere deltakere (13-18 år) og foreldre (13-15 år), og de som ønsker det kan få mer utfyllende informasjon og samtykkeskriv fra prosjektmedarbeidere.

Komiteen har ingen innvendinger til at prosjektet gjennomføres slik det fremstilles.

Vedtak

Komiteen godkjenner prosjektet i henhold til helseforskningsloven § 9 og § 33.

Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden.

Tillatelsen gjelder ti 31.12.2022. Av dokumentasjonshensyn skal opplysningene likevel bevares inntil 31.12.2027. Opplysningene skal lagres avidentifisert, dvs. atskilt i en nøkkel- og en opplysningsfil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder «*Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren*»

Sluttmelding og søknad om prosjektendring

Prosjektleder skal sende sluttmelding til REK sør-øst på eget skjema, jf. hfl. § 12.
Prosjektleder skal sende søknad om prosjektendring til REK sør-øst dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang

Du kan klage på komiteens vedtak, jf. forvaltningslovens § 28 flg. Klagen sendes til REK sør-øst B. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst B, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Komiteens avgjørelse var enstemmig.

Med vennlig hilsen

Ragnhild Emblem
professor, dr. med. leder
REK sør-øst B

Mariann Glenna Davidsen
rådgiver

Kopi til:

- Universitetet i Agder ved øverste administrative ledelse

Appendix 4: Figures and tables for the introductory review

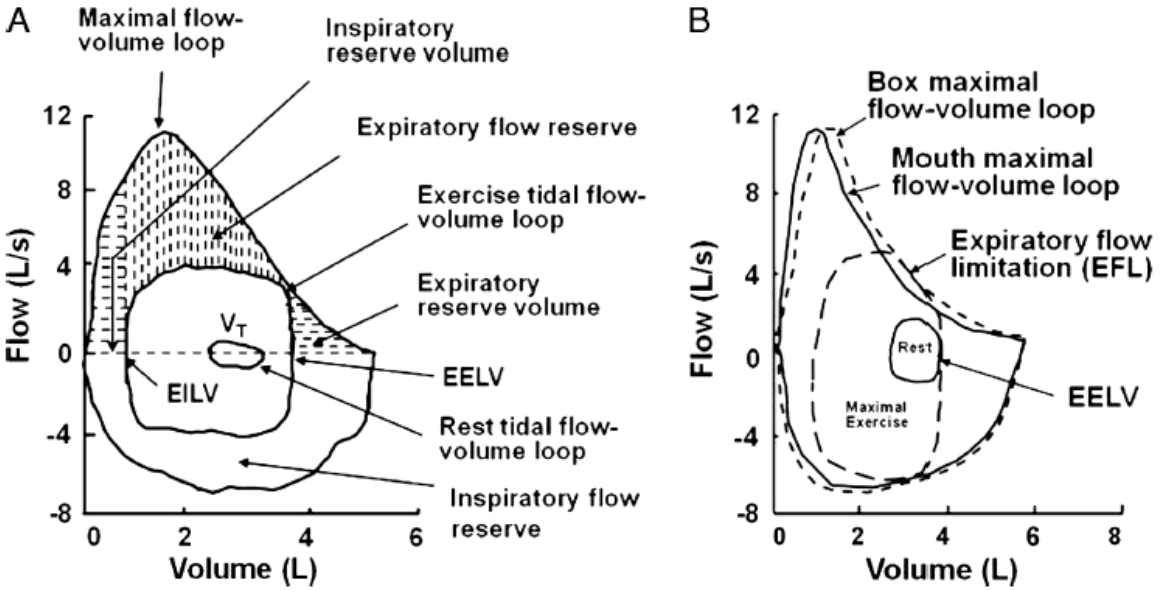

Figure 1.Ventilatory changes from rest (A) and exercise (B). Taken with permission from: *Exercise and Sport Sciences Reviews,* Volume 41 Issue 1. Tony Babb. Exercise Ventilatory Limitation: The Role of Expiratory Flow Limitation. p. 14.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3529766

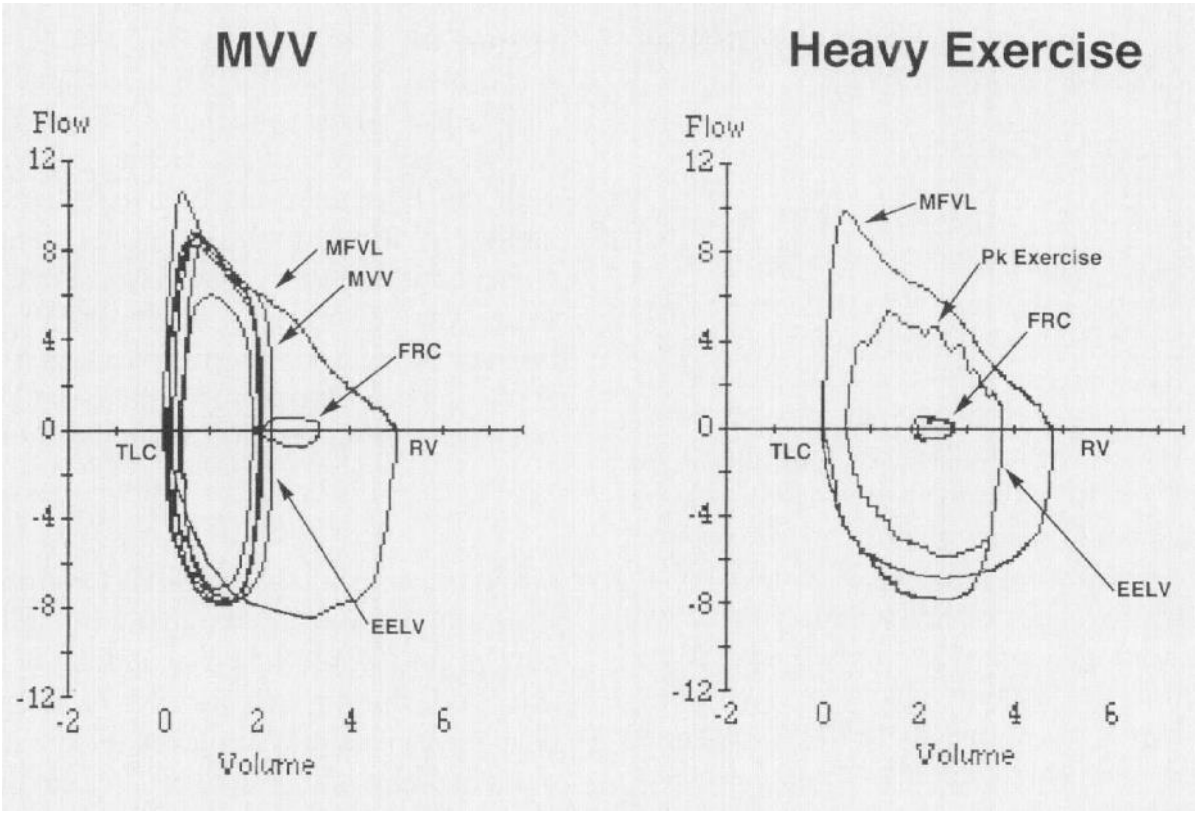

Figure 2: The difference in breathing pattern and EELV when the MVV maneuver is performed (left) relative to the same persons at peak exercise intensity (right). Reprinted from *CHEST*. Bruce D. Johnson, Idelle M. Weisman, .Jorge R Zeballos, Ken C Beck. Emerging Concepts in the Evaluation of Ventilatory limitation During Exercise: the exercise tidal flow volume-loop. Volume 116, Issue 2 p. 493 Copyright (1999) with permission from Elsevier.

Appendix 5: Submission guidelines for BMJ Open Respiratory Research

Original Research

Original Research should follow the basic structure of Abstract, Introduction, Methods, Results, Discussion, References, and tables and figures as appropriate.

Word count: up to 4000

Abstract: up to 300

Tables/Illustrations: up to 5

References: up to 100

Formatting checklist

1. **Author information:** Have you got an ORCID iD (from the 28th November 2018 a majority of BMJ Journals will be mandating ORCID iDs for all submitting authors at the time of article submission). Have you provided details of all of your co-authors? Is the information that you have entered into ScholarOne the same as the information on the manuscript title page?
2. **Manuscript length and formatting**: Have you provided your abstract in the correct format? Have you supplied any required additional information for your article type, such as key messages? Have you checked that your manuscript doesn't exceed the requirements for word count, number of tables and/or figures, and number of references?
3. **Tables**: Are your tables in an editable format? Have you embedded them into the main word document? Have they been cited in the text? Have you provided appropriate table legends? Have you uploaded any lengthy tables as supplementary files for online publication?
4. **Figures**: Have you uploaded figures separately from the text? Have they been supplied in an acceptable format and are they of sufficient quality? Are they suitable for black and white reproduction (unless you intend to pay any required fees for colour printing)? Have the files been labelled appropriately? Have the figures been cited in the text? Have you provided appropriate figure legends?
5. **References**: Have all of the references been cited in the text?
6. **Supplementary files**: Have you supplied these in an acceptable format? Have they been cited in the main text?
7. **Statements**: Have you included the necessary statements relating to author contributorship, competing interests and funding, data sharing, patient consent and ethical approval?
8. **Acknowledgements:** Have you acknowledged all contributors who do not meet the criteria for authorship? Have you acknowledged if your work has been previously presented at a conference/published as a conference abstract?
9. **Suggested reviewers:** Have you suggested reviewers for your paper (if required by the journal)?
10. **Research reporting checklists**: Have you either provided the appropriate statement for your study type, or explained why a checklist isn't required?

11. **Reproducing figures:** Have you obtained permission from the copyright holder to re-use any previously published material? Has the source been acknowledged?

Title page

This is excluded for the journal *BMJ Quality and Safety* which operates triple-blind peer review.
The title page must contain the following information:

- Title of the article.
- Full name, postal address, e-mail and telephone number of the corresponding author.
- Full name, department, institution, city and country of all co-authors.
- Word count, excluding title page, abstract, references, figures and tables.
-

Keywords

Authors can usually opt to (or are required to) choose keywords relevant to the content of the manuscript during the submission process. This assists in the identification of the most suitable reviewers for the manuscript. The selected keywords should also be included in the abstract itself.

The manuscript must be submitted as a Word document.PDF is not accepted.
The manuscript should be presented in the following order:

- Title page.
- Abstract, or a summary for case reports (Note: references should not be included in abstracts or summaries).
- Main text separated under appropriate headings and subheadings using the following hierarchy: BOLD CAPS, bold lower case, Plain text, Italics.
- Tables should be in Word format and placed in the main text where the table is first cited. Tables should also be cited in numerical order.
- Acknowledgments, Competing Interests, Funding and all other required statements.
- References. All references should be cited in the main text in numerical order.
Figures must be uploaded as separate files (view further details under the Figures/illustrations section). All figures must be cited within the main text in numerical order and legends should be provided at the end of the manuscript.

Online Supplementary materials should be uploaded using the File Designation "Supplementary File" on the submission site and cited in the main text.
Please remove any hidden text headers or footers from your file before submission.

Style

Acronyms and abbreviations should be used sparingly and fully explained when first used. Abbreviations and symbols must be standard. SI units should be used throughout, except for blood pressure values which should be reported in mm Hg.
Whenever possible, drugs should be given their approved generic name. Where a proprietary (brand) name is used, it should begin with a capital letter.

Figures/illustrations

Images must be uploaded as separate files. All images must be cited within the main text in numerical order and legends must be provided (ideally at the end of the manuscript).

Colour images and charges

For certain journals, authors of unsolicited manuscripts that wish to publish colour figures in print will be charged a fee to cover the cost of printing. Refer to the specific journal's instructions for authors for more information.
Alternatively, authors are encouraged to supply colour illustrations for online publication and black and white versions for print publication. Colour publication online is offered at no charge, but the figure legend must not refer to the use of colours.
Detailed guidance on figure preparation

File types

Figures should be submitted in TIFF, EPS, JPEG or PDF formats. In EPS files, text (if present) should be outlined. For non-vector files (eg TIFF, JPEG) a minimum resolution of 300 dpi is required, except for line art which should be 1200 dpi. Histograms should be presented in a simple, two-dimensional format, with no background grid.
For figures consisting of multiple images/parts, please ensure these are submitted as a single composite file for processing. We are unable to accept figures that are submitted as multiple files.
During submission, ensure that the figure files are labelled with the correct File Designation of "Mono Image" for black and white figures and "Colour Image" for colour figures.
Figures are checked using automated quality control and if they are below the minimum standard you will be alerted and asked to resupply them.
Please ensure that any specific patient/hospital details are removed or blacked out (e.g. X-rays, MRI scans, etc). Figures that use a black bar to obscure a patient's identity are NOT accepted.

Tables

Tables should be in Word format and placed in the main text where the table is first cited. Tables must be cited in the main text in numerical order. Please note that tables embedded as

Excel files within the manuscript are NOT accepted. Tables in Excel should be copied and pasted into the manuscript Word file.
Tables should be self-explanatory and the data they contain must not be duplicated in the text or figures. Any tables submitted that are longer/larger than 2 pages will be published as online only supplementary material.

References

Authors are responsible for the accuracy of cited references and these should be checked before the manuscript is submitted.

Citing in the text

References must be numbered sequentially as they appear in the text. References cited in figures or tables (or in their legends and footnotes) should appear at the end of the reference list to avoid re-numbering if tables and figures are moved around at peer review/proof stage.
Reference numbers in the text should be inserted immediately after punctuation (with no word spacing)—for example,[6] not [6].
Where more than one reference is cited, these should be separated by a comma, for example,[1, 4, 39]. For sequences of consecutive numbers, give the first and last number of the sequence separated by a hyphen, for example,[22-25]. References provided in this format are translated during the production process to superscript type, and act as hyperlinks from the text to the quoted references in electronic forms of the article.
Please note that if references are not cited in order the manuscript may be returned for amendment before it is passed on to the Editor for review.

Preparing the reference list

References must be numbered consecutively in the order in which they are mentioned in the text.
Only papers published or in press should be included in the reference list. Personal communications or unpublished data must be cited in parentheses in the text with the name(s) of the source(s) and the year. Authors should request permission from the source to cite unpublished data.
Journals from BMJ use a slightly modified version of Vancouver referencing style (see example below). Note that The BMJ uses a different style.

BMJ reference style

List the names and initials of all authors if there are 3 or fewer; otherwise list the first 3 and add ‘et al.’ (The exception is the Journal of Medical Genetics, which lists all authors). Use one space only between words up to the year and then no spaces. The journal title should be in italic and abbreviated according to the style of Medline. If the journal is not listed in Medline then it should be written out in full.
Check journal abbreviations using PubMed
Check citation information using PubMed

Example references

Journal article
13 Koziol-Mclain J, Brand D, Morgan D, et al. Measuring injury risk factors: question reliability in a statewide sample. *Inj Prev* 2000;6:148–50.

Chapter in book

14 Nagin D. General deterrence: a review of the empirical evidence. In: Blumstein A, Cohen J, Nagin D, eds. Deterrence and Incapacitation: Estimating the Effects of Criminal Sanctions on Crime Rates. Washington, DC: National Academy of Sciences 1978:95–139.

Book

15 Howland J. Preventing Automobile Injury: New Findings From Evaluative Research. Dover, MA: Auburn House Publishing Company 1988:163–96.

Abstract/supplement

16 Roxburgh J, Cooke RA, Deverall P, et al. Haemodynamic function of the carbomedics bileaflet prosthesis [abstract]. *Br Heart J* 1995;73(Suppl 2):P37.

Electronic citations

Websites are referenced with their URL and access date, and as much other information as is available. Access date is important as websites can be updated and URLs change. The "date accessed" can be later than the acceptance date of the paper, and it can be just the month accessed.

Electronic journal articles

Morse SS. Factors in the emergency of infectious diseases. *Emerg Infect Dis* 1995 Jan-Mar;1(1). www.cdc.gov/nciod/EID/vol1no1/morse.htm (accessed 5 Jun 1998).

Electronic letters

Bloggs J. Title of letter. *Journal name* Online [eLetter] Date of publication. url eg:
Krishnamoorthy KM, Dash PK. Novel approach to transseptal puncture. *Heart* Online [eLetter] 18 September 2001. http://heart.bmj.com/cgi/eletters/86/5/e11#EL1

Legal material

Toxic substances Contro Act: Hearing on S776 Before the Subcommittee of the Environment of the Senate Comm. on Commerce, 94th Congress 1st September (1975).
Washington v Glucksberg 521 US 702 (1997)

Law references

The two main series of law reports, Weekly Law Reports (WLR) and All England Law Reports (All ER) have three volumes a year.
For example:
Robertson v Post Office [1974] 1 WLR 1176
Ashcroft v Mersey Regional Health Authority [1983] 2 All ER 245
R v Clarence [1868] 22 QBD 23
Wimpey Construction UK Ltd v Poole (1984) Times, 3 May
There are good historical precedents for the use of square and round brackets. Since 1891, round ones have referred to the date of the report, square ones to the date of publication of the report. Apart from not italicising the name of the case, we use the lawyers' style; be careful with punctuation. Here are some more examples:
Caparo Industries plc v Dickman and others [1990] 1 All ER 568-608.
R v Clarence [1888] 22 QBD 23.
Finlayson v HMAdv 1978 SLT (Notes) 60
Block v Martin (1951) 4 DLR 121
Official Journal of the European Communities: at the top of the page it gives the No, vol, and page and, at the other side of the header, the date.
The abbreviation for the title is given in parentheses under the title. Jiggle these elements around to get, eg:
Council Directive of 14 June 1989. Offical Journal of the European Communities No L 1989 June 28:181/44-6. (89/831/EEC.

Digital Object Identifier (DOI)

A DOI is a unique string created to identify a piece of intellectual property in an online environment and is particularly useful for articles that are published online before appearing in print (and therefore have not yet been assigned the traditional volume, issue and page number references). The DOI is a permanent identifier of all versions of an article, whether

raw manuscript or edited proof, online or in print. Thus the DOI should ideally be included in the citation even if you want to cite a print version of an article.

How to cite articles with a DOI before they have appeared in print

1. Alwick K, Vronken M, de Mos T, et al. Cardiac risk factors: prospective cohort study. *Ann Rheum Dis*Published Online First: 5 February 2004. doi:10.1136/ard.2003.001234

How to cite articles with a DOI once they have appeared in print

1. Vole P, Smith H, Brown N, et al. Treatments for malaria: randomised controlled trial. *Ann Rheum Dis*2003;327:765–8 doi:10.1136/ard.2003.001234 [published Online First: 5 February 2002].

PLEASE NOTE: RESPONSIBILITY FOR THE ACCURACY AND COMPLETENESS OF REFERENCES RESTS ENTIRELY WITH THE AUTHOR.

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Requestor type	Individual
STM publisher name	
Portion	Figures/table/illustration
Number of figures/tables/illustrations	1
Figures/tables/illustrations used	Figure 1
Author of this Wolters Kluwer article	No
Title of your thesis / dissertation	Changes in breathing reserve and expiratory flow limitation at peak exercise intensity after a 10-weeks exercise intervention in adolescents with asthma
Expected completion date	May 2019
Estimated size(pages)	1
Requestor Location	Anette Nielsen ******** Oslo, other Norway Attn:
Total	0.00 USD
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