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Title

"The difference in pulmonary function, lung volume, and diffusion capacity and the effects of body composition in asthmatic and healthy endurance athletes and controls"

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Abstract

Background: Elite endurance athletes who daily exercise in unfavorable environments such as cold or polluted air is in increased risk for developing asthma. However, endurance athletes are reported to have greater pulmonary function and lung volumes compared to non-athletes. Mechanisms behind the observed differences are unclear. Fat and muscle mass are believed to affect pulmonary function in obese subjects, but the association in athletes is not known.

Objective: The main objective was to compare pulmonary function, lung volume and diffusion capacity (DLco) between endurance athletes with/without self-reported asthma competing within cross-country skiing and swimming and healthy controls. The second objective was to investigate the possible association between body mass index and body composition upon pulmonary function in the same population.

Methods: An observational case-control study was conducted with 25 asthmatic endurance athletes, 37 healthy endurance athletes, and 27 healthy non-athlete controls. Pulmonary function was measured by spirometry. Body plethysmography was used to measure lung volumes and the single breath method was used to measure diffusion capacity (DLco). Body composition was measured with Inbody 720, bio-electrical impedance analysis.

Results: The healthy athletes had significantly higher pulmonary function (FEV_1, MVV) and DLco compared to controls. No differences were observed between asthmatic athletes and healthy athletes or asthmatic athletes and controls. Fat-mass had a significant negative association to DLco. Muscle mass had a significant positive association to DLco.

Conclusion: The findings from the present study show that healthy endurance athletes have superior pulmonary function and diffusion capacity compared to controls. No differences were observed between asthmatic athletes and healthy athletes or asthmatic athletes and controls. Diffusion capacity has a significant association to fat and muscle mass in the same population.

Keywords: asthma, endurance athletes, body composition, pulmonary function, FEV_1, DLco

Abbreviations		Unit
AT	Anaerobic threshold	-
BC	Body composition	-
BHR	Bronchial hyperresponsiveness	-
BIA	Bioelectrical impedance analysis	-
BMI	Body mass index	kg/m^2
CO_2	Carbon dioxide	mm/Hg
DLco	Diffusion capacity	ml/mmHg/min
EIA	Exercise induced asthma	-
EIB	Exercise induced bronchoconstriction	-
FEV_1	Forced expiratory volume in one second	$l \bullet min^{-1}$
FEF50	Average forced expiratory flow in 50 % of FVC	$l \bullet min^{-1}$
FEV_1/FVC	percent of FVC breathed out during the first second	%
FFM	Fat-free mass	kg
FM	Fat-mass	kg
FVC	Forced vital capacity	$l \bullet min^{-1}$
Hb	Hemoglobin	g/dL
l	Liters	-
ml	Milliliter	-
MVV	Maximum voluntary ventilation	$l \bullet min^{-1}$
O_2	Oxygen	mm/Hg
PA	Physical activity	-
PaO_2	Partial pressure for oxygen in arterial blood	mm/Hg
$PaCO_2$	Partial pressure for carbon dioxide in arterial blood	mm/Hg
PF	Pulmonary function	-
PFT	Pulmonary function test	-
SD	Standard deviation	-
SSM	Skeletal muscle mass	kg
TLC	Total lung capacity	l
VFA	Visceral fat area	cm^2
VO_{2max}	maximal oxygen uptake	$ml \bullet kg^{-1} \bullet min^{-1}$

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1.0 Introduction

1.1 Background of the present study

While the prevalence of asthma has increased significantly during the past decades (2), evidence of decreased physical activity (PA) worldwide is growing (3, 4). PA, defined as "any bodily movement produced by skeletal muscles that requires energy expenditure", is known to reduce asthma symptoms, increase quality of life and lifespan in both young and old asthmatic subjects (5), and to protect against asthma (6). PA is also known to decrease the risk for diabetes mellitus type 2 (DM2) and coronary vascular diseases (CVD) (7). Nevertheless, only 20 % in Norway meets the recommended level of physical activity for at least 30 minutes of moderately intense activity on five days per week (8).

Results from earlier studies have not shown any differences in pulmonary function (PF) between athletes with and without exercise-induced asthma (EIA) at rest, but they have first of all included cold-weather athletes (9). Findings shows that healthy competitive swimmers have increased PF compared to land based athletes, and non-athletes (10) as well as higher diffusion capacity (DLco) compared to non-athletes (11). Obese subjects have also been showed to have increased DLco (12, 13). The mechanisms behind the observed difference in PF and DLco are unclear. Elite endurance athletes who daily exercise with high minute ventilation in unfavorable environments such as cold or polluted air have an increased risk for developing respiratory diseases like asthma and bronchial hyperresponsiveness (BHR) (14). Asthma and BHR is especially high among elite athletes in swimming and cross-country skiing (15).

Asthma is associated with obesity (16) which has been reported to negatively influence PF independent of asthma (17), while muscle mass has been reported to influence PF positively in healthy non-athletes (18). There are findings suggesting a positive relationship between amount of fat-free mass (FFM) and PF in patients with chronic obstructive disease (COPD) (19) and in asthmatic children (20). PA and body composition (BC) can therefore be seen as components affecting PF both in young and old non-athletes (21). Authors suggest that most likely, the loss of muscle mass is associated with loss of respiratory muscle mass (22, 23). Together with asthma symptoms and increased abdominal fat this might impair PF (12). Decreased PF is also found to be related to increased risk of illness and mortality (24). Findings suggest that aerobic exercise

both may increase FFM (25), train the respiratory muscles (26), and increase PF (27) which could explain the observed decrease in the age-related deterioration in PF, seen in physical active older subjects (28). FFM has also been shown to have a positive relationship to DLco in healthy subjects (18). No research to the author knowledge is however done on investigating the influence of body mass index (BMI) and BC upon PF, lung volume, and DLco in healthy and asthmatic endurance athletes, competing in cross-country and swimming.

The purpose of this study was therefore to investigate possible differences in PF, lung volume and DLco between endurance athletes with/without self-reported asthma and healthy controls. The study is first of its kind to also investigate the influence of BMI and BC upon PF, lung volume and DLco in highly trained athletes with/without self-reported asthma and healthy controls. Investigating possible differences between groups with different PA level, health status, and BC may be helpful in finding possible mechanisms explaining why some athletes have superior PF and DLco. Findings have already suggested that severe obesity decreases, while greater FFM increases PF in non-athletes (29). The effect of BMI and BC upon PF, lung volume, and especially DLco in athletes is not known.

1.2 Objectives and aims

The main objective is to compare pulmonary function, lung volume, and diffusion capacity (DLco) between endurance athletes with self-reported asthma to endurance athletes without self-reported asthma, and to healthy controls. The second objective is to investigate possible effects of body mass index (BMI) and body composition (BC) upon pulmonary function, lung volume, and DLco in the same population.

1.3 Research aims

1. To asses pulmonary function, lung volume, and diffusion capacity in self-reported asthmatic endurance athletes, healthy endurance athletes, and healthy controls
2. To investigate possible differences in pulmonary function, lung volume, and diffusion capacity in the same population as described
3. To asses body mass index and body composition in the same population as described
4. To investigate if body mass index and body composition are associated with pulmonary function, lung volume, and diffusion capacity in the same population as described

1.4 Study hypotheses

Based on the objectives and research aims, as well as review of previous literature, the hypotheses of the present study are:

1.

$H0_1$= There are no differences in PF, lung volume or DLco between the three groups.

$H1_1$= There is a significant difference in PF, lung volume, and DLco between the three groups.

2.

$H0_2$= There is no association between BMI and BC compared to PF, lung volume or DLco in the same population.

$H1_2$= BMI and BC are associated with PF, lung volume, and DLco in the same population.

2.0 Theoretical background

2.1 The pulmonary system

To better understand the mechanisms behind PF, a short introduction into the work of the pulmonary system will be presented.

The pulmonary system or the respiratory system in healthy humans includes the airways, two lungs, and the respiratory muscles, such as the diaphragm, which together with the ribs attaches the lungs. The internal intercostal muscles and the external intercostal muscles also contribute during inspiration and expiration together with the diaphragm. The diaphragm is a large dome-shaped muscle and is the primary muscle involved in active inspiration (30). The diaphragm has similar structure and fatigue resistance as skeletal muscles (31). The main task of the pulmonary system is to supply oxygen (O_2) to the blood through inspiration, and remove carbon dioxide (CO_2) through expiration. Nasal cavity, mouth, pharynx, larynx, trachea, and tracheal branches (bronchi and bronchioles) are included in the upper and lower airways as the image below shows.

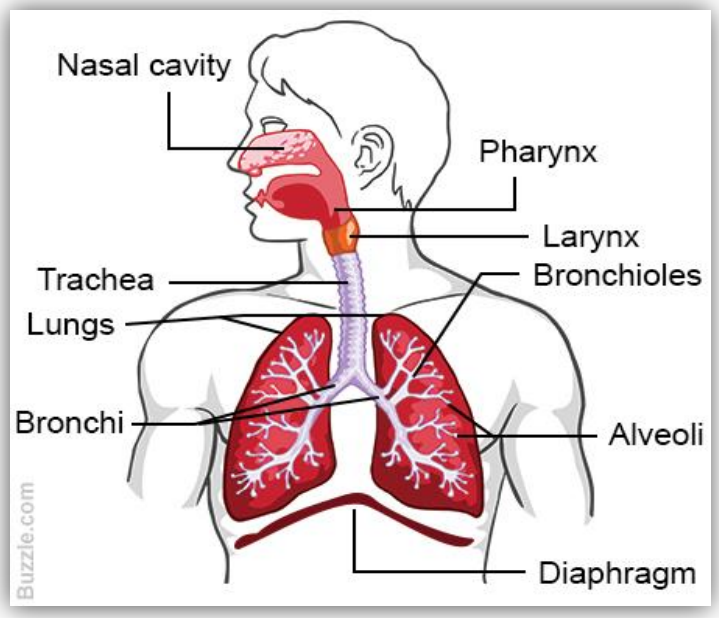


Figure 1: Shows an overview of the upper and lower airways
[http://www.buzzle.com/articles/human-respiratory-system-functions.html 2013]

The process of respiration can be divided into; ventilation, gas exchange between the alveoli air and the blood, perfusion which includes the transport of O_2-rich blood, and gas exchange between the blood and the cells. Ventilation is in other words the continuous process of air travelling from the atmosphere and the alveoli in the lungs. The transport of air into the lungs is called inspiration, while the transport of air out of the lungs is called expiration (32). This is achieved by help from the respiratory muscles which expand the lungs. Air flows from the atmosphere into the lungs when the chest expands and lung pressure is less than the atmospheric pressure. Due to elasticity and rebound effect in the lungs, exhalation during rest occurs mainly passive, except from forced maneuvers for instance during exercise (32). The respiratory muscles are then recruited to assist during exhalation.

Looking closer into the process, we see that the bronchioles enters the alveoli (tiny air sacs), where each alveoli is surrounded with a network of capillaries. The blood runs from the right side of the heart through the pulmonary arteries, into this network of capillaries (tiny blood vessels). Blood gases exchanges between the air in the alveoli and the blood in the pulmonary capillaries called the vascular bed of the lungs (Figure 2). This process is possible due to the difference in pressure for oxygen/carbon dioxide (PaO_2/$PaCO_2$) which is arising from changes in lung volume between the air in the lungs and the air in the atmosphere. This process is called diffusion and requires that both the circulation to the lungs and the distribution of oxygen into the lungs are satisfactory (32).

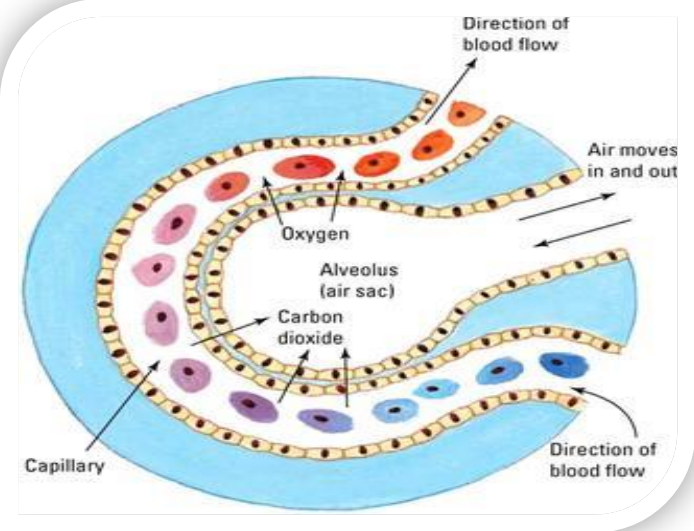


Figure 2: Image of the process called diffusion, were the gas exchange takes place, with the alveoli sacs, surrounded by one capillary ***[http://yr8science2011.wikispaces.com]***

The blood is supplied with O_2 from the alveoli air and exchanged with CO_2 to the alveoli air. The blood which leaves the alveoli is then O_2-rich and transported from the lungs to the cells where it is needed (32). Gas moves from high partial pressure to low partial pressure due to differences in O_2 and CO_2 concentration within the alveoli and the blood. Patrial pressure is the pressure in each gas. The partial pressure of O_2 (PaO_2) is a measurement of oxygen in arterial blood and is higher in the air sacs than in the blood circulating the lungs, making the diffusion of O_2 possible. O_2 attaches to hemoglobin (Hb) in the red blood cells after passing through the alveolar membrane, tissue fluid, blood vessel wall, and blood plasma (33). The partial pressure for CO_2 ($PaCO_2$) is higher in the blood, making the diffusion of CO_2 the opposite way possible (13).

2.2. Measuring pulmonary function

2.2.1 Spirometry

Pulmonary function (PF) is naturally a product of the pulmonary system. PF is of great value due to its simplicity in assessment of health and respiratory diseases like asthma and as a predictor for mortality (24, 34). Pulmonary function tests (PFT) measures how much air that can be inhaled and exhaled by the lungs, how well the lungs deliver oxygen to the blood, and to some degree measure the strength of the breathing muscles (35). PFT may help in diagnosing asthma, cyctic fibrosis, COPD, and also to check how well treatments, such as asthma medicines, are working. Age, sex, height, ethnic origin, and general health are the most important determinants in PF. PA and lifestyle, muscle mass, geographic factors, pollutants, and socio-Economical status are other factors that have an impact on PF (36). Results from recent studies indicated however that BMI and BC should be taken into account when measuring PF (18, 20). PFT includes; spirometry, body plethysmography and somewhat also diffusion capacity (DLco). Spirometry, invented in 1846 by Hutchinson is the most common PFT. Together with the body plethysmograph which measure lung volumes and specific airway resistance (sRaw). Both are widely used to assess respiratory diseases like asthma and COPD (33).

Spirometry is a helpful tool in clinical use, in detecting and follow up lung diseases in both healthy individuals and patients. It is used to determine how an individual inhales or exhales

volumes of air as a function of time (33). The test measures first of all the rate at which the lung changes volume during forced breathing maneuvers (1). Different PF measures or lung capacities can then be measured during a spirometry maneuver, for instance forced vital capacity (FVC), which measures the total volume of air that can be exhaled during a maximal forced expiration effort (33). Forced expiratory volume in 1 s (FEV_1) is the maximal volume of air exhaled during the first second of a forced expiration from a position of full inspiration, usually 75 % of FVC (Figure 3). ≥80 % of predicted is accepted as the lower limit of normal values for FEV_1 and FVC (37). Percentage of predicted (%) are reference values from large populations, based on the subjects gender, age, height, and ethnic origin (36). The use of %of predicted values (% pred.) allows comparison with other studies, which may have a different balance of sex and age. The FEV_1/FVC ratio expresses the percent of FVC that can be breathed out during the first second (33), and is often reduced in asthmatic patients. The forced expiratory flow (FEF) in 25-75 % and 50 % of FVC (FEF25-75% and FEF50) is the average forced expiratory flow between 25% and 75% of the FVC, or percentage of FVC. It can be helpful in the diagnosis of an obstructive disease and can give information about airway resistance. A reduction of less than 60 percent of predicted values may confirm airway obstruction (1). Both FEF25-75 % and FEF50 is highly dependent on the validity of the FVC measurement and expiratory effort (1).

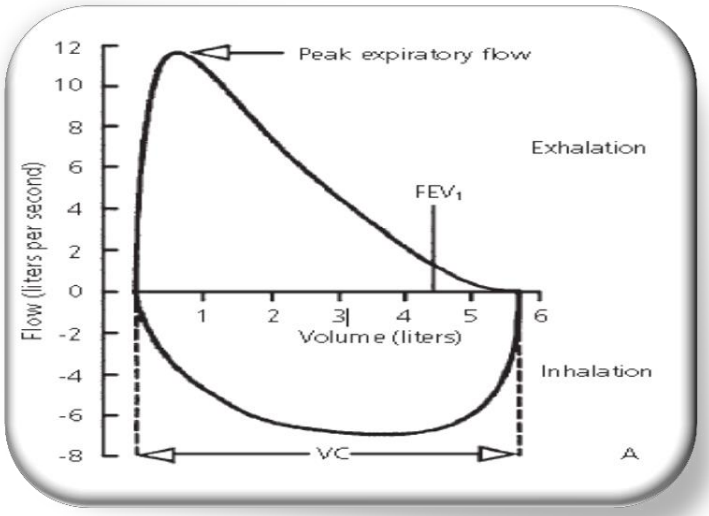
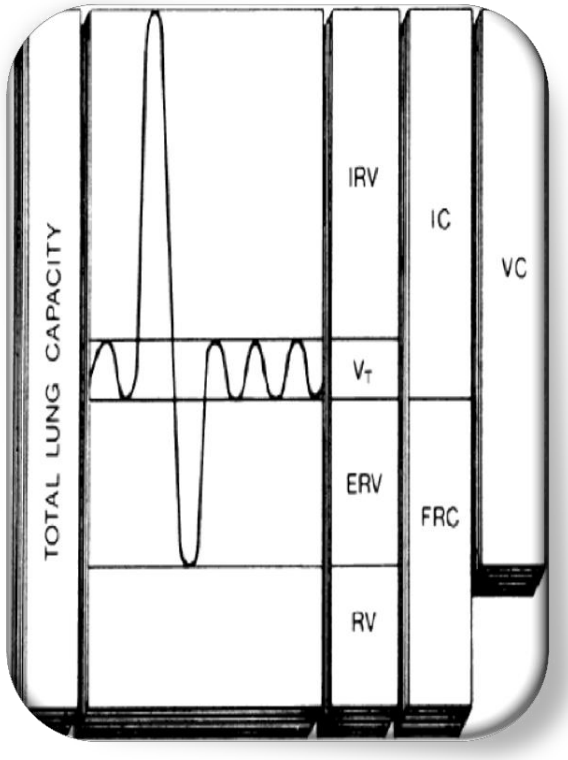


Figure 3: A normal spirometric flow diagram (1)

2.2.2 The maximal voluntary ventilation (MVV)

MVV is part of the spirometry measurement and is measured by a maximal voluntarily breathing maneuver which last for 12 seconds in a standing position. The result is extrapolated to 60 seconds to determine the MVV per minute and reported in liters per minute. MVV maneuver can

be used to confirm obstructive and restrictive conditions during maximal ventilation (similar to high intensity training) and is approximately equal to the FEV_1•40 (1).



TLC: Total lung capacity; the volume of air in the lungs at maximal inflation.

IRV: Inspiratory reserve volume; the maximal volume of air inhaled from end inspiration.

V_T: Tidal volume; the volume of air inhaled or exhaled during each respiratory cycle

ERV: Expiratory reserve volume; the maximal volume of air exhaled from end expiration

RV: Residual volume; the volume of air remaining in the lungs after a maximal exhalation

IC: Inspiratory capacity; the maximal volume of air that can be inhaled from the resting expiratory level

FRC: Functional residual capacity; the volume of air in the lungs at resting end expiration

VC: Vital capacity; the largest volume measured on complete exhalation after full inspiration

Figure 4: An overview of lung volumes that creates the total lung capacity (TLC) measured with body pletysmography [1]

2.2.3 Body plethysmography

Spirometry is established as the gold standard when measuring PF. It can however not provide information on lung residual volume (RV) and total lung capacity (TLC) (Figure 4). The measurement of the lung volumes are divided into four volumes; tidal volume, expiratory reserve volume, inspiratory reserve volume, and residual volume (1) (Figure 4). Those four volumes together create the total lung capacity (TLC) which is the volume of air in the lungs at maximal

inflation. Normal TLC value is between 80-120 % of predicted values (1). Body plethysmography allows too determine these and other characteristics, such as sRaw and thoracic gas volume (Vtg). The sRaw is increased in asthmatics, and falls with successful asthma therapy (38). These measures are recorded during breathing at rest with body plethysmography and not by forced maneuvers. That is why, body plethysmography and spirometry both should be performed to give a complete image of the subjects pulmonary function (39).

The whole-body plethysmograph is a chamber which in shape and volume resembling a glass-walled telephone box (Figure 8). It is usually called the "body box". During measurement the box is closed with an airtight seal, except for a small controlled leak that is used to stabilize the internal pressure. The subject is provided with sufficient oxygen during testing (39). The principle relies on detecting changes in box pressure in combination with either changes of mouth pressure or with flow rate under defined breathing conditions, making it possible to determine lung volumes and sRaw (39). A pressure transducer can measure both the pressure inside the box as well as the mouth pressure during a so called shutter maneuver. When investigating the sRaw, the shutter mechanism is used to block the airflow. After ERV the subject are told to place his/her fingers on the cheeks, and the mouthpiece is closed as the subject is instructed to perform a series of gentle pants at a given frequency (0.5-1.0 Hz) against a shutter occluding the airways. After 3-5 technically satisfactory panting maneuvers recorded, the shutter is opened and the test is done.

2.2.4 Diffusion capacity (DLco)

The air in the pulmonary system moves to areas of the lung that is easily accessible. In patients or athletes with obstructive lung diseases like asthma and COPD, uneven ventilation may occur. This may prevent the inhaled air to be distributed throughout the lung area. Consequences are reduced supply of O_2 gas and poor ventilation of old gas in the affected areas. Normal gas exchange is dependent on ventilation and perfusion in each part of the lung. Processes disturbing this balance is when blood comes in contact with poorly ventilated alveoli's, or if good ventilated alveoli's does not come in contact with circulating blood, called ventilation-perfusion mismatch

(33). The diffusion capacity to carbon monoxide (DLco) determines the quality of the above mentioned gas transfer in the lungs.

DLco calculated either as ml/mmHg/min or as % of predicted value can be measured using different methods. A standard procedure is to use a test gas which determines the quality of gas transfer in the lungs or how fast O_2 passes from the lungs into the blood stream. This method is called the single breath method (33). The test gas consists of 0,3 % methane (CH4), 0,3 % carbon monoxide (CO), 21 % O_2, and 78,4 % nitrogen (N_2). DLco is determined from the known amount of CO gas inhaled and the measured concentration gas exhaled (13). DLco is calculated after inspiration and expiration of the described test gas, and are measured by the amount of CO and CH4 in the expired gas relative to the inhaled gas, after a breath hold of 8-10 seconds. CH4 do not diffuse into the blood but is diluted, and is mixed with the remaining air in the lungs, the RV. The degree of dilution of CH4 is used to calculate the effective alveolar volume (VA) which is the volume of air in the alveoli air. CO diffuses into the blood with additional dilution. Amount of CO that diffuse into the blood are determined by gas exchange area between alveolus and capillary, wall thickness (membrane) from alveoli to erythrocyte, the membrane conductivity, the blood in the capillaries, available quantity hemoglobin (Hb) and the reaction rate of CO to Hb (40). Normal DLco are reported to be between 60-120 % of predicted values, based on subjects gender, age, height, and ethnic origin (1).

2.2.5 Effects of physical activity upon pulmonary function, lung volume and diffusion capacity

To better understand possible differences in PF between healthy and asthmatic athletes and non-athletes as well as possible effects of PA and exercise, a short introduction into earlier research will be described.

Longitudinal studies have showed that subjects with higher levels of PA had lower incidence of asthma, suggesting that PA is a possible protective factor against asthma development (6). However, a 10-year follow up study on three elite athletes in cross-country skiing showed deterioration in PF over the years by high intensive exercise in dry and cold air.

The skiers had objective signs of airflow limitations during intense exercise, and FEV_1 was significantly decreased below % pred. after 9-12 years follow up (41).

A study included adult asthmatic patients. They completed 10 weeks of high intensity exercise, and was then followed up for three years (42). No change was seen in PF after three years. However, number of hospital admissions and symptoms were reduced, and it is likely that the tolerance for physical activity may increase in asthmatics subjects due to improved physical fitness (43). Some argue that regular physical activity and exercise influences PF positively in healthy subjects (28, 44). Standard endurance conditioning trains the respiratory muscles, in the same way as the skeletal muscles (45). Therefore, endurance trained subjects could be expected to have well-trained respiratory muscles which may increase PF. 12 weeks of aerobic exercise has shown to increase PF in obese subject (46). Studies which have found increases in PF often explain the results due to loss of fat-mass that may occur after periods of exercise, as in the study by Mendelson et al., (2012) (46). Loss of weight is however found to decrease DLco in obese men (12). Sedentary subjects are reported to have higher BMI and fat-mass than physical active subjects (47). Womack et.al (2000) divided groups into weight loss intervention and aerobic exercise (48). The weight loss group increased FEV_1, TLC, and RV after decreasing weight by 11 %. The aerobic exercise group increased aerobic capacity (VO_{2max}) by 14 % with no changes in PF. There are several studies showing that, strength exercises, alone or together with aerobic exercise, improves fat-free mass (FFM) independent of diet in overweight and obese males and females (25). One could therefore hypothesize that athletes especially those who train more than 10 hours/week have higher FFM than sedentary subjects. Findings suggest just how important that might be. There are results showing that both higher levels of PA and higher amount of FFM is associated with higher average PF (49). Mechanisms behind this are not yet understood, but it seems that the loss of FFM is associated with loss of respiratory muscle mass (22). The respiratory muscles, especially the diaphragm, contribute in active inspiration and exhalation, and can therefore be seen as extremely important for PF. Loss of FFM is not only associated with inactivity, but also with ageing (50).

The effect of endurance training on PF in healthy French cyclists and triathletes were investigated with no reduction or improvements after a year of endurance training (51). A Turkish study reported on the other hand increased PF after a period of 24 weeks with aerobic exercises in older

non-athletes (52). They also concluded that FFM correlated significantly with PF (FEV_1 and FVC). In an earlier study, higher VC, IRV, and ERV were found in runners compared to gymnast, and higher FVC were found in swimmers compared to gymnast (53). Vedala, Paul & Mane (2013) found increased FVC, FEV_1, and FEV_1/FVC in Indian marathon runners compared to healthy sedentary subjects (44). Hagberg, Yerg & Seals (1988) found however no differences in PF between healthy young endurance athletes compared to age-matched sedentary controls (28). The results from the same study did however show higher PF in the older athletes compared to age-matched sedentary controls. Over 10 years of prolonged exercise was suggested to have altered the decline in PF that is associated with ageing (31).

Swimmers are found to have superior PF in several studies (10, 27, 54-56). VC, RV, IC, and FRC is found to be higher in 11 female college swimmers compared to cross-county skiers and non-athletes (55). Increased FEV_1, FVC, TLC, and DLco is also observed in competitive swimmers after a period of detraining followed by 12 weeks of standard swim training (27). VC, TLC, and FRC are also observed to increase in female competitive swimmers after 12 weeks of swim training (54). A Greek study found increased FEV_1 in highly trained national swimmers compared to non-national swimmers, land based athletes, and sedentary subjects (10). When the years of training was controlled for, the difference between the national and non-national swimmers was no longer significant. This suggests that the years of swim training or the earlier the age at which training start may have an influence on FEV_1. Armour, Donnelly & Bye (1993) found however increased PF in swimmers but with no effect of the years of swimming (56). The study does not exclude the influence of genetics, but it is suggested that swimmers have greater chest width, containing increased number of alveoli's (56). The study by Armour et al., (1993) also showed greater VC, TLC, and DLco in swimmers (56).

2.3 Body composition

Body weight, height and body composition do have an important position in the evaluation of a person's health (57). A short introduction in human body composition (BC) is needed to fully understand the impact BMI and BC may have upon PF.

The body consist of six main elements; water, fat (lipids), proteins, carbohydrate, bone minerals, and soft tissue minerals. Fat and carbohydrate are the primary fuels used by the body during exercise. Lipids are substances that are generally insoluble in water, while muscles contains a large amount of water (58). BC are usually divided into fat mass (FM) and fat-free mass (FFM) by a classic two-components model (59). The terms FFM and lean body mass (LBM) are often used interchangeably in the literature. Both explain the amount of fat-free mass. However, while FFM contains no fat, LBM contains some essential fatty acids. FFM includes organs, soft tissues, and skeletal tissues which contains proteins, minerals, and a large amount of water, about 73,8% (58). Low level and loss of FFM are related to impaired functional capacity and decreased energy expenditure. High energy intake combined with decreased energy expenditure is a risk factor for gaining FM (58). Amount of FFM is important during exercises for instance during pushing or carrying as well as during running (58).

Human muscles are divided into skeletal, cardiac and smooth muscles. The cardiac muscles form the wall of the heart while smooth muscles are located around the internal structures in the body such as intestines. Skeletal muscles are attached to the bones and can contract voluntarily (59). Skeletal muscle mass (SMM) consist of protein and water, with absence of bone minerals, and cardiac and smooth muscles.

Deposition of FM is often described in two distinct patterns. A central pattern (upper body) typically seen in men, and a peripheral pattern (lower body) who is more typically seen in women (60). FM or adipose tissue can be divided into internal or external fat. Internal fat refers to the fat found around organs (visceral fat) and fat found deep into the muscles. External fat or subcutaneous fat is found underneath the skin. Increased FM is found to be associated with diseases like DM2 and CVD, while FFM may work the other way, as a protector (61). Visceral fat (VF) is found to be more metabolic active and is associated with higher risk for diseases, for instance CVD than subcutaneous fat. Subcutaneous fat is however a stronger predictor for insulin sensitivity than VF, often seen in men with noninsulin dependent DM2 (62). Fat is twice as

energy dense as carbohydrate or protein. Excess FM adds only non-force producing mass and increases the metabolic cost during PA as for instance in running (59). A diet should however include enough fat, as it is very important for good health (58). Essential fatty acids are essential in physiological functions as blood pressure, heart rate and immune response (58). Recommended FM levels for young female athletes is between 23-28 %, and 10-15 % for young male athletes (58).

2.3.1 Methods for measuring body composition

Measuring BC includes wide specters of methods. Methods which are used in earlier studies where the relation between BC and PF, lung volumes or DLco are investigated will be explained here. A greater emphasize is placed on the measurement used in the present study. The three first methods mentioned is highly inaccurate and are dependent on factors such as equations, equipment and trained test leaders. The latter one is highly reliable but is not without risk (radiation), as well as it is expensive and time consuming, and with need of a specifically-trained technician (63).

Body mass index (BMI)

A simple way of measuring BC is by using body mass index (BMI) (64). BMI is the relationship between height and weight ($kg*m^2$) and the World Health Organization (WHO) has classified individuals as Table 1 shows. BMI is valuable when used in large populations, although with limitations. BMI does not provide information on BC (65). In muscular subjects BMI is less reliable, since higher BMI may arise due to increased muscle mass.

Table 1: An overview of BMI classification set by the World Health Organization (WHO) (66)

BMI ($kg*m^2$)	Classification
<18	Underweight
18,5-24,9	Normal healthy range
25-29,9	Overweight
30-34,9	Obesity class I
35-39,9	Obesity class II
>40	Obesity class III

Waist to hip ratio (WHR)

The circumference of the waist to the circumference of the hips (waist to hip ratio or WHR) is a more valid estimator of BC, because it is possible to investigate abdominal obesity, by using a flexible metal tape around the abdomen of subjects in a standing position. The waist can be defined as the minimal abdominal circumference located between the lower edge of the rib cage and the iliac crests. The iliac crest is the curved bone at the top of the pelvic. The hip can be defined as the maximal circumference around the gluteal muscles below the iliac crests (67).

Skinfold thickness

Measuring the skinfold thickness is a popular method for estimating FM and FFM and is used in several studies (52, 68, 69). It is done by taking four sites of the body (triceps, chest, abdomen, thigh), and measure the adipose tissue by using a caliper. Percentage of body fat may then be estimated by using different equations. There are developed standard techniques to reduce measurement errors and increase the reliability. It is important to measure as accurately as possible, as measuring only 1 inch from the measurement point can result in significant different results (57). The method is therefore highly dependent on experienced test leaders.

Dual energy x-ray absorptiometry (DEXA)

Dual energy x-ray absorptiometry (DEXA) is known as one of the most reliable method for measuring BC and are used clinically often in hospitals and medical laboratories (70). DEXA uses X-ray to measure bone mineral density (BMD) and BC while subject is in a supine position, using high and low energy photons (electromagnetic radiation). BC is measurable with X-rays since fat, bones, and muscle varies in density and chemical composition, making it possible to distinguish between the tissues.

Bio-electrical impedance (BIA)

Measuring FFM and FM can be calculated from single- and multiple-frequency bio-impedance analysis (BIA). Measurement of body impedance may indirectly provide information on the body's tissue content (71). BIA offers a precise and inexpensive alternative to DEXA, with minimum need for specially trained technicians. The multi-frequency impedance technique uses a spectrum of electrical frequencies to predict the intracellular water (ICW) and extracellular water (ECW) in the body. Low-level frequencies (1–50 kHz) rely on the conductive properties of extracellular fluid, whereas, high-level frequencies (250 kHz), measures both ICW and ECW (72). The human body consists of 5 distinct cylinders (arms, trunk, and legs) which the impedance technique measures separately. This allows for regional analyses of muscle mass, in addition to total FFM, FM, and TBW. Adjustment of bioelectrical data for height allows estimation of TBW, and these equations are applied subsequently to predict TBW, which is converted to FFM. The relationship between bioelectrical data and TBW is influenced by the age range investigated and other characteristics of the population (73). BIA equations are population specific and may predict FM poorly in individuals with different physique and health status (edema), with errors of about 8 % (73).

Inbody 720 is an example of a noninvasive measurement which adopts multi-frequency bio-impedance, and uses an 8-point tactile electrode system (74). Inbody 720 sends weak electrical signals through the body while the subject is standing on two electrodes and gripping around one electrode in each palm (73). The machine analyses the density of the body and calculates FM and FFM, based on the principle that FFM contains virtually all the water and conducting electrolytes in the body, providing a good electrical pathway, whereas FM containing tissues that produce a poor electrical pathway (71). The electrical impedance (Z) consists of two components, resistance (R) and reactance (Xc). Xc is a measure of body cell mass (BCM) while R is a measure of total body water (TBW) (75). From the determined impedance a number of BC parameters can be estimated, such as kg and % of FFM, SMM, and FM as well as the amount of fat found around organs (visceral fat area or VFA) measured as cm^2. Inbody 720 defines abdominal obesity as VFA of more than 100 cm^2.

Inbody 720 has proved to be a suitable alternative to DEXA, which is widely used for assessing BC (76). Inbody 720 is a valid estimator of FFM and total FM in men (71). Results also shows

that Inbody 720 may well be used when measuring visceral fat, as it significantly correlated with those of CT-scans in adult cancer patients (63). Although one study concluded that Inbody 720 only should be used in subjects with a BMI up to 34 (77) a recent validation study on FM and FFM using Inbody 720 compared to DEXA showed an almost perfect correlation in severe obese women (BMI >40) (76). A Finnish study showed that Inbody 720 measures an average of 2-6 % lower FM than DXA in men with normal BMI. The difference was smaller in obese men (78). Inbody 720 is also found to underestimate FM and overestimate FFM compared to DXA in obese patients (76). Inbody 720 is not based on statistical data of any specific population. It is capable of accurately assessing BC in people with very different physical physique, whether obese, elderly or athletic.

When different investigators follow the same standardized procedure by use of BIA, and uses the same device, population, and criterion, similar prediction errors and prediction equations have been reported (79). With proper standardization of methods, instruments, and subject preparation, assessment of BC can quickly, easily, and relatively inexpensively provide accurate and reliable estimations.

2.3.2 Effects of BMI and body composition upon pulmonary function, lung volume, and diffusion capacity

BC can, as described, influence health and sport performance, but can it influence the respiratory system? In patients with COPD, respiratory muscle strength are found to be closely associated with body weight, LBM, and PF (19).

Increased BMI are associated with higher levels of FM, which has been reported to influence PF negatively. This is first of all during expiration. Decreased FVC and FEV_1 in middle-aged subjects with increased BMI is reported (68). In younger people, increased BMI may be associated with an increased PF (muscularity effect), whereas in older people, higher BMI is associated with decreased PF (adiposity effect) (67). Population surveys using BMI have reported lower levels of PF among subjects with high BMI (80), in addition to longitudinal findings of accelerated loss of PF with increasing weight (81, 82). Although BMI do have an undeniable

effect on PF, it loses the importance of predicting spirometry results after adjusting for age and height (83).

Evidence that increased WHR is associated with decreased PF in males, shows that abdominal obesity may well influence the ventilation. (67, 84, 85), This is also reported after measuring BC by skinfold thickness to estimate body fat and muscle mass (52, 68, 69). A Turkish study actually found a significant inverse correlation between FFM and FVC and FEV_1 in both men and women, with lower PF in those who had low FFM (52). BMI and percentage of FM had a significant inverse relationship on PF in the same study. VF are showed to negatively influence FVC in 86 patients with systemic sclerosis (SS), a disease which often leads to muscle atrophy (86). Rossi et al., (2008) found VF to inversely correlate with both FVC and FEV_1 in elderly men and women (29). A Finnish study measuring BC by BIA on healthy non-athletes explained the increased DLco (% pred.) seen in healthy subject with increased SSM and LBM (18). No other spirometry results where influence by SSM or LBM in the same study. A different study found however that increased FM was associated with increased DLco (% pred.) (12).

2.3.3 The mechanisms of body composition

Greater PF in athletes may be a product of higher FFM, which might be due to higher levels of PA. This is however only assumptions, since little research exist on BC and PF in athletes. But findings on grip strength and it's positively association with FEV_1 and FVC (87) may suggest that the amount of FFM is associated with greater FEV_1 and FVC (22, 88). Findings on increased PF together with increased inspiratory muscle strength may also explain the associating between BC and pulmonary function (27). The amount of FFM is linked to amount of respiratory muscle mass (22).

Excess body fat do have a mechanical effect on the diaphragm by impeding the ability of the muscle to descent into the abdominal cavity during inspiration (Figure 5), and on the compliance in the chest wall (68). Obesity may alter the relationship between the lungs, chest wall and diaphragm. Increased FM, especially upper body obesity may also reduce lung volume and impairing the airway and thoracic skeletal muscle function (12). Increased body weight might

also reduce the ability to perform the MVV maneuver well, due to its rapid and deep breathing demand (89). This is observed in severe obese subjects (12).

FFM may indirectly influence PF as the respiratory muscles are recruited for vocalization and upright posture as seen when performing different Valsalva-like maneuvers during lifting, carrying and reaching (90). That might be the reason why athletes have been reported to exhibit superior forced expiration (FEV_1, FVC) compared to sedentary individuals (10). The respiratory muscles have an important role in active inspiration and greater respiratory muscles strength may also increase the forced expiration.

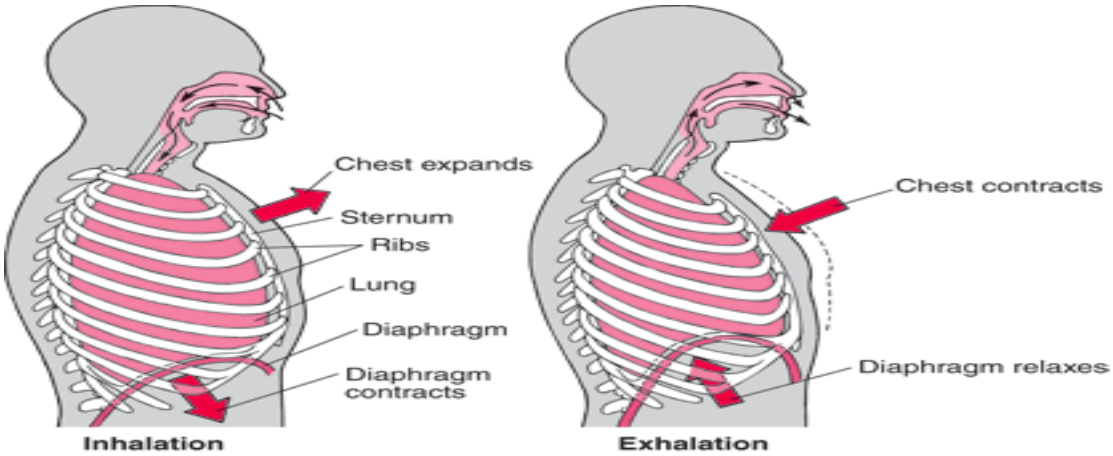


Figure 5: Shows the diaphragm's role during breathing. Abdominal obesity may prevent the muscle to contract into the abdominal cavity during active inspiration and forced expiration
[www.merckmanuals.com/home/lung_and_airway_disorders/biology_of_the_lungs_and_airways/control_of_breathing.html]

2.3.4 Why suspect differences in pulmonary function and diffusion capacity?

PF has been found to differ between subjects with different height, gender, age, and weight (68). However, studies which have controlled for these factors, still find differences in PF (10, 28, 91). Several studies has successfully showed that healthy swimmers do have higher PF and DLco, both compared to land based athletes (10) and to healthy controls (11, 55).

Recent studies have however indicated that both BMI and BC influences PF (18, 83). There seems to be a positive relationship between PF, and BMI, as shown in asthmatic children (20). It

is also demonstrated that weight loss and thereby reduced BMI may explain the improvement in PF in male and female adults (68, 92). Studies using DEXA (29, 83), skinfold thickness (69) and BIA (18) all show an inversely relationship between FM and PF, and a positive relationship between PF and increased FFM. Increased respiratory muscle mass is shown to have a strong correlation upon FEV_1 in patients with normal PF (93). Therefore, increased FFM and reduced FM may explain the increased PF seen in athletes compared to sedentary controls (10, 28, 91). The PF of subjects with asthma are reported to be affected during periods of exercise in environment with allergens or pollution (94), although results shows no significant differences between athletes with/without asthma at rest (9).

Any tendency towards reduced TLC will also decrease rather than increase DLco (12). Previous findings from Ray, Sue & Wasserman (1983) shows that DLco (% pred.) increases with obesity, and decreases after weight loss (12). Increased DLco is interestingly also found in competitive swimmers, both compared to non-athletes (11) and to % of predicted values (56, 95). There is also evidence that obese subjects have increase pulmonary capillary blood, which increases DLco (13). Patient with obstructive lung diseases like asthma are however found to have uneven ventilation. This might prevent the inhaled air to be distributed throughout the lung area. Consequences are reduced supply of O_2 gas and poor ventilation of old gas in the affected areas, which could reduce DLco (33).

2.4 Asthma and bronchial hyperresponsiveness (BHR)

Asthma is one of the most common diseases in childhood and adolescence affecting around 300 million individuals worldwide (96). Although a wide range of definitions are used in the literature today, asthma can be defined as a chronic inflammatory disorder of the airways with bronchial hyperresponsiveness (BHR) and variable bronchoconstriction (97). The prevalence of asthma has been reported in 20.2 % of 10-year-old children in Norway (98), in approximately 20 % of British children and 8-13.5 % in children from Western European Mediterranean (99). Asthma is mostly associated with family history, allergy, smoking, and obesity in the general population (100). Low birth weight may also contribute to childhood asthma (101).

The term exercise-induced bronchoconstriction (EIB) or exercise-induced asthma (EIA) is used when physical exercise itself is the cause of asthmatic symptoms (94). EIA or EIB are terms that refer to the transient narrowing of the airways following vigorous exercise (94). EIA and EIB are often used together and the differentiation in the international literature is inconsistent. EIA is used to describe symptoms provoked by moderate to strenuous exercise with presence of cough, wheezing, shortness of breath and or chest pain. The symptoms often occur 5 minutes after physical exertion, and lasting up to 15-30 minutes after the exercise (102). EIA has been reported to occur in 50-80 % of people with asthma, and about 9 % in individuals without a history of asthma symptoms (102). EIA is reversible with asthma medications (97). EIB describes the reduction in FEV_1 of at least 12% after a standardized exercise test, often after running on a treadmill for 6-8 minutes with an intensity as high as 95 % of predicted maximum heart rate (94).

2.4.1 Bronchial hyperresponsiveness (BHR)

Bronchial hyperresponsiveness (BHR), common in asthmatic subjects and patients with COPD, is defined as an increase in sensitivity to a wide variety of airway narrowing stimuli such as allergens, pollution, chlorine in the pool or cold air (103). In asthmatic subjects, this hypersensitivity is accompanied by excessive degrees of airway narrowing (104). BHR can be measured by standardized bronchial challenges, indirectly by an exercise test, voluntary dry air hyperpnoea or inhalation of mannitol, or directly to a pharmacological stimulus, such as the transmitter substance methacholine or the mediator substance histamine (14). BHR may also be

present in subjects without asthma (104). Reports on swimmers found a prevalence of 48 % to histamine (105). A Canadian study showed a prevalence of 69 % in swimmers and 28 % in cold-air athletes, which included cross country skiers and speed skaters (106). These results in addition to reports on decreasing asthma and airway inflammation after end of athletic swimming careers, indicate that asthma is induced by systematic training for some athletes (107). Heavy physical performance have also been reported to increase BHR in swimmers (108). One study found increased BHR in young skiers right after the coldest period of the year, suggesting that cross-country skiers exercising in subfreezing climate are in risk of developing BHR (109).

2.4.2 Prevalence of asthma in athletes

Asthma is the most common chronic medical condition in Olympic athletes with a prevalence of 7-8 %, including both winter and summer sports (110, 111). The prevalence of asthma and BHR among elite athletes in swimming (15) and cross-country skiing (112) is especially high. A group of elite Swedish cross-country skiers had a prevalence of either asthma symptoms or BHR high as 80 % (112). Symptoms are often more prevalent than diagnosed asthma in skiers. Results from a study showed a prevalence of 14 % of diagnosed asthma in cross country skiers compared to 5 % in a control group (113).

In 1989, the first evidence of heavy exercise causing increase in BHR was reported (108). BHR to the mediator substance histamine was increased after a 3000 m swimming bout in both healthy and asthmatic children, and the exercise intensity, measured as increase in serum lactate, correlated significantly with the increase in BHR. This was followed by reports of EIA and BHR among participants in the 1998 American Olympic National team for winter sports, including gold medalists (114). Similar findings among Olympic athletes using asthmatic medication was later reported (115). In a more recent study, the evidence of asthma was as high as 60 % in swimmers and 29 % in cold-weather athletes compared to 17 % of non-athletes (106). A Finish study examined the difference in asthma between male and female swimmers, found a prevalence of 19 % in both genders (116). Although the prevalence of BHR and/or EIA is shown to be higher in swimmers compared to winter sport-athletes (106, 117), self-reported respiratory symptoms seems to be more frequent among cross-country skiers. In a study by Bougault,

Turmel & Boulet (2010), 53 % swimmers compared to 72 % winter sport athletes (including cross-country skiers) reported having exercise-induced symptoms, with chough being the most frequent symptom. Stenfors (2010) showed a prevalence of 17 % of self-reported symptoms of EIA after physical activity in elite cross-country skiers (118). The interesting finding from this study is that the reported symptoms also were found in healthy elite cross country-skiers.

2.4.3 Mechanism of exercise-induced asthma in athletes

It is first and foremost a high exercise volume (> 20 hrs/week) and not moderately dosed (10-20 hours/week) exercise volume that is a risk factor for the development of asthma (119). A large meta-analysis indicated that exercise, even large amounts, can protect against asthma in non-athletes (6). On the other hand, it is believed that athletes who repeatedly exercise with high minute ventilation (V_E) in environments with high exposure of cold air or pollution are in increased risk of developing asthma. Inhalation of cold air, traffic air pollution (diesel exhaust particles), nitrogen oxides (NO) and ozone (O_3), as well as chlorine particles in ambient air of indoor swimming pools has been shown to be unfavorable for the athlete's respiratory health (14). This may explain why winter sport athletes, such as cross-country and biathlon skiers, as well as swimmers are among those athletes with highest prevalence of self-reported symptoms and BHR (117, 120).

Research on asthmatic subjects shows that moderate physical activity at low temperatures rather than moderate activity at room temperature leads to significant decreases in FEV_1 (121). Healthy subjects have been reported to withstand the cold much better, with no decrease in PF variables after testing VO_{2max} during inhalation of cold air (122). It is suggested that cold air exerts its effects through its low water content and participate in the drying of the respiratory mucosa (123). Loss of heat and water from the airways is believed to be the two main causes of EIA, initiating the release of a series of mediators that eventually will induce bronchoconstriction after exercise (94). When V_E increases from 8-12 liters at rest and up to 200 L during maximal physical activity, the airway heat- and water loss will increase as inhaled air is warmed up to 37 °C and fully saturated with water before reaching the alveoli's. The risk for the small airways to become dehydrated and cooled down increases as colder and/or drier the air gets. Long periods of

hyperventilation also increase the risk for deposition of airborne allergens, chlorine, and other irritants particles in the lower airways (51). Maximal exercise may lead to hyperventilation, which in turn leads to mechanical stress on the bronchial wall of the airways, as well as cooling and drying of the airways. This may eventually lead to the accumulation of inflammatory cells and mediator release that can lead to BHR and bronchoconstriction (124-126).

Loss of water from the airway mucosa increases the osmolality in the extracellular fluid of the bronchial mucosal membranes causing an intracellular increase in ion concentration through movement of water from inside the cell to the extracellular space (123). The frequent exposure to cold, dry air at high ventilation rates can cause a thickening of the bronchial sub epithelial membrane, which also is observed in asthmatic subjects (127). These processes may lead to the release of mediators and cause bronchoconstriction.

2.4.4 Asthma and parasympathetic activity

The parasympathetic nervous system which is one of three divisions of the autonomic nervous system, is important for instances in processes conserving energy and slowing down the heart rate. Parasympathetic activity is also been reported to be associated with EIA and are reported to be higher among endurance athletes compared to healthy controls (128). During high V_E rates, a cooling of both the central and peripheral parts of the respiratory tract stimulates parasympathetic nerve receptors which lead to an increase in parasympathetic activity through the vagus nerve. This stimulates smooth bronchial muscles, causing a reflex bronchoconstriction as well as a reflex vasoconstriction of the bronchial venules to conserve heat (129, 130). When exercise stops and the need for conserving heat ceases, a reflex vasodilatation of the bronchial venules occur, thus potentially contributing to a mucosal edema (108). It has also been suggested that autonomic function is related to the development of BHR and asthma and that different prevalence of asthma symptoms in athletes within the same sport may be explained by differences in parasympathetic activity (131).

3.0 Methods

3.1 Study design

This study is part of a PhD-project investigating mechanisms behind asthma in endurance athletes called "Mechanisms for asthma in athletes" (the MASI-study). The population and test procedures are somewhat similar, although this is an individual study. Only those tests that are needed to answer the hypotheses are included in the present study. That is also reflected in the test protocol. This is an observational case-control study with three groups, consisting of 25 asthmatic athletes (group 1), 37 healthy athletes (group 2) and a healthy, non-athlete, control group of 27 subjects (group 3). I will compare group 1 with group 2 as well as group 1 and 2 with group 3, in regard to the current aims and hypotheses presented. The groups will also be divided by respective sports with/without self-reported asthma in the analysis. PF measurements included in this study are FEV_1, FVC, FEF50, FEV_1/FVC, and MVV, as well as lung volume (TLC) and diffusion capacity (DLco). These values will be compared to BMI and BC, were SMM, FFM, FM, and VFA are included. Data collection was performed according to the test protocol. The subjects attended the laboratory on two separate days separated by at least 24 hours, but not more than 3 weeks in between visits, required by the "MASI-study". The three groups all conducted the same test procedure.

3.2 Literature research

Relevant literature search were conducted through Medline, ScienceDirect, and SPORTDiscus. Search words were asthma, asthma in athletes, asthma and cross-country skiing, asthma and swimming, pulmonary function in athletes and non-athletes, pulmonary function and body composition. Relevant papers in English who included either/both athletes or non-athletes were then included, and are discussed and compared with findings reported in this study.

3.3 Subjects

The study population included endurance athletes at national and international level (preferable cross-country skiers and swimmers) with and without self-reported asthma as well as control subjects (non-athletes) who was sought out to be at the same age, both male and female. The diagnosis of asthma and EIA in athletes is clinical and based on history of symptoms, physical examination of signs indicating the presence of bronchial obstruction and variability in lung function spontaneously or due to bronchodilators (94). The main symptoms of asthma are recurring episodes of bronchial obstruction and the term current asthma is used when at least one episode of asthma has occurred during the last year. Subjects were placed in the three different groups after filling out a questionnaire about asthma and allergy (see Appendix). If subject reported having asthma and/or asthma symptoms and/or use of anti-asthmatic medication as well as training ≥10 hours/week, they were placed in the asthmatic group. Athletes who trained ≥10 hours/week, not reporting asthma or symptoms of asthma were placed in the healthy athlete group. Healthy subjects training ≤5 hours were placed in the control group. After been given oral and written information about the study objectives and methods, written informed consent was obtained from all participants (see Appendix). The subjects were able to withdraw consent at any time throughout the course of the trial. The subjects were informed that their medical care not would be adversely affected if they decline to participate in this study. Parent/guardian provided consent if the participant was under 18 years.

3.4 Recruitment

The first consecutive competitive athletes with asthma and healthy athletes, as well as healthy subjects who agree to participate in the study were recruited. Athletes were recruited from sport clubs in the south-eastern part of Norway, as well as from the national teams (junior, recruit and senior) through Olympiatoppen in Oslo, Norway. Control subjects were recruited through the Norwegian School of Sport Sciences and the University of Oslo.

3.5 In- and exclusion criteria

Subject inclusion criteria

- Male and females aged 15-40 years
- Endurance athletes competing at a high national or international level with and without asthma (preferable cross-country skiing and swimming) training ≥10 hours/week
- Asthma: self-reported presence of asthma, EIA and/or asthma symptoms and/or use of anti-asthmatic medication
- Healthy controls training ≤5 hours/week

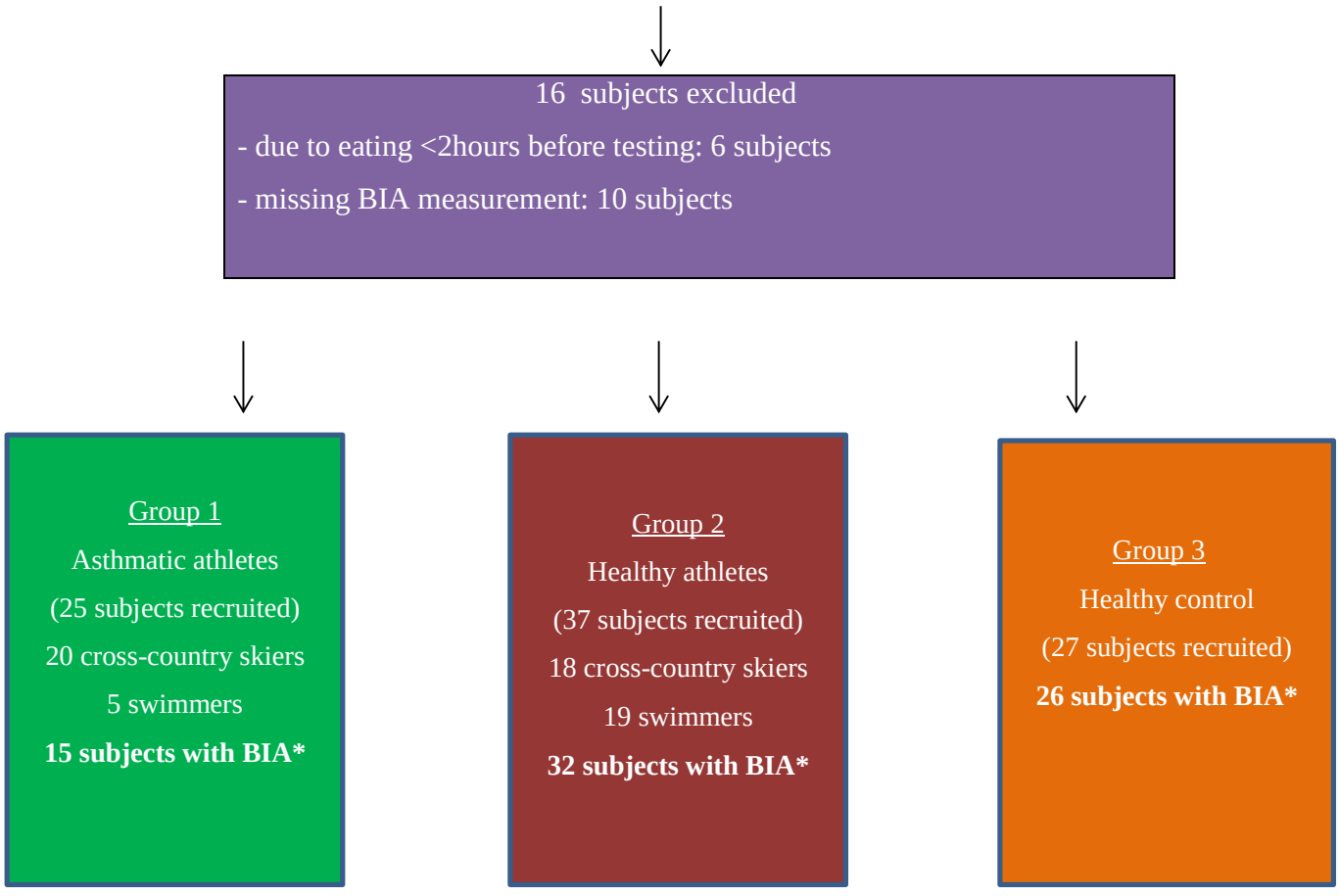
Subject exclusion criteria

- Controls competing in a professional sport
- Asthmatic or symptomatic controls
- Acute respiratory illness in the last three weeks before testing
- Chronic cardiac, neurological or psychiatric disorders, as well as recent stroke or heart attack
- Training at the same day before testing
- Eating, drinking coffee, smoking or drinking large amount of fluid ≤2hours before testing
- All that, in the opinion of the test leaders, would place the subject at increased risk

3.6 Measurements

3.6.1 Test Protocol

Day 1	1. Anthropometric measurements and body composition 2. Spirometry 3. DLco 4. Whole-body phletysmography (body box) 5. MVV
Day 2	1. Spirometry, DLco, body box, and MVV if not conducted at day 1 2. Anthropometric measurements and body composition if not conducted at day 1 3. Questionnaire (modified $AQUA_{2008}$)



*Bioelectrical impedance analysis (Inbody 720)

3.6.2 Anthropometric measurements and body composition

Anthropometric measurements and body composition variables were obtained from all participants, wearing light clothing and no shoes or socks. Height was first measured in a standing upright position with a digital stadiometer (SECA 217, SECA, Germany). Body composition measurement was performed with the BIA device Inbody 720 (Body Composition Analyzer, Biospace Co. Ltd., Soul, Korea) with standardized procedures including a minimum of 2-hour fasting and no drinking before measurement. An eight-polar tactile-electrode was set in contact with both anterior and posterior aspects of each sole, and left and right thumbs and palms. Inbody 720 uses 6 frequencies (1, 5, 50, 250, 500, and 1000 kHz) and produces 30 impedance values for 5 body segments, arms, trunk and legs. The electrodes were disinfected before each measurement. The subject was instructed to stand upright with both feet on two electrodes as well as holding two electrodes in his/her hands with arms resting down (Figure 6). Instructions were given by test leaders (master students or PhD-student). To increase reliability the measurement was conducted twice, as recommended (79). The measurements are then presented as means. The test takes a few minutes and was carried out at day 1. The variables analyzed from Inbody 720 were weight, BMI ($kg*m^2$), FFM, SSM, FM, and VFA. Inbody 720 does not measure VFA in young adolescence and children below the age of 18. Valid measurement on VFA in athletes and non-athletes above the age 18 were included and is further explained as VFA (cm^2). FMM, SSM, and FM were included for all ages and are further explained in % of body weight.

Figure 6: Image of subject standing with both feet on two electrodes while holding two electrodes in each palm measuring body composition with the Inbody 720

3.6.3 Pulmonary function (Spirometry)

Spirometry was measured by maximum expiratory flow volume loops according to European standards (132), and recorded as forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, and forced expiratory flow 50 % (FEF50). Spirometry was measured using MasterScreen PFT v.570 Pneumo Jeager® (Würzburg, Germany) and calibrated before each test day. Standardized reference values are used, that calculates the obtained values compared to age, gender, height and ethnic origin (133). Subjects were seated, wearing nose clips and performed maximal expiratory efforts until 3 flow-volume loops were within 3 % of each other (Figure 7). FEV_1 and FVC will further be explained as % pred.

Figure 7: Image of subject performing spirometry and DLco seated wearing a nose clip with MasterScreen PFT v.570 Pneumo Jeager® (Würzburg, Germany)

3.6.4 Maximal voluntary ventilation (MVV)

Maximal voluntary ventilation (MVV) was measured by voluntarily breathing maximally for 10 seconds using MasterScreen PFT v.570 Pneumo Jeager® (Würzburg, Germany). The instrument was calibrated before each test day. Subjects were wearing nose clips and asked to breathe as rapidly and deeply as possible. Subjects were standing upright and told to use the upper body to help inhale and exhale as much as possible for 10 seconds. The best of three trials was used to assess MVV. The result was multiplied by six to determine the MVV per minute, and will further be explained in % pred. MVV together with FEV_1, FVC, FEV_1/FVC, and FEF50 is reported as pulmonary function in the present study.

3.6.5 Diffusion capacity (DL_{CO})

DL_{CO} was measured using the single breath method according to current guidelines (13). In a seated position and wearing a nose clip, the subject was breathing normally through a mouthpiece (MasterScreen PFT v.570 Pneumo Jeager® Würzburg, Germany) before inhaling to total vital capacity (IVC) and slowly exhaled to residual volume (RV). Thereafter the subject performed an inspiratory vital capacity maneuver (IVC) inhaling the gas mixture followed by an 8 seconds breath hold. The IVC maneuver should last > 2.5 s, but not longer than 4 s and the inhalation should be ≥90% of FVC in order for the test to be valid. Diffusion capacity was determined from the known amount of CO gas inhaled and the measured exhalation gas. Dead space volume, approx. 0.75 L, was eliminated from analysis. Measurements were performed until 2 valid tests had a difference of <10%. Each measurement was separated by 4 min wash-out periods. The result from this test will further be explained in % pred.

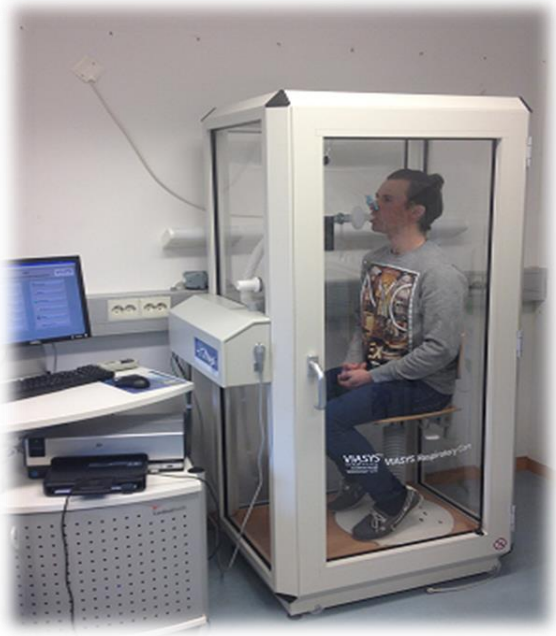


Figure 8: Image of subject placed in the body box, seated with a nose clip measuring Whole-body phletysmography with Sensor Medics Vmax 229 series with Autobox (VIASYS Healthcare Inc, Yorba Linda, CA, USA)

3.6.6 Lung volumes and airway resistance (Whole-body phletysmography)

Lung volumes were measured by a body plethysmograph which assess thoracic gas volume (Vtg) and the functional residual capacity (FRC) in the lungs. Measurements was performed on a Sensor Medics Vmax 229 series with Autobox (VIASYS Healthcare Inc, Yorba Linda, CA, USA) and recorded as total lung capacity (TLC). The procedure was performed in accordance with the European Respiratory Society (ERS) (134) and standardized reference values were used (132). The subject was placed inside a sealed chamber, seated with both feet touching the floor, and instructed to breathe normally through a single mouthpiece while wearing a nose clip (Figure 9). A baseline level of FRC was established from at least four stable tidal breaths. The subjects

was then asked to perform a slow inspiration to total vital capacity (IVC) followed by an Expiratory Reserve Volume (ERV) maneuver. Measurements are performed until 2 valid tests have a difference of <10% and the average value were calculated for further analysis. TLC is the only variable included in the analysis, and will further be explained in % pred.

3.7 Questionnaires

The questionnaire used in the study was the modified $AQUA_{2008}$, developed for the assessment of asthma, allergy and other respiratory symptoms (135) (see Appendix). The questionnaire was only used to evaluate if the subject were to be placed in the asthmatic group 1, in the healthy group 2, in the control group 3 or to be excluded from the study.

3.8 Data collection

All results were continuously listed on result sheets while each test was conducted. The results were then later listed on a computer. Data registrations and the result sheets was anonymized and made inaccessible to all persons other than those responsible for the project. Data for this study includes age, gender, height, body mass, body composition, and pulmonary variables. Clinical data was entered into a data capture system. The data system includes password protection and internal quality checks.

3.9 Statistical methods

Statistical analyses were performed with Statistical Package of Social Sciences (SPSS) version 21, SAS (v. 9.3) and Microsoft Excel 2010. Microsoft Excel 2010 was also used to make figures, and Microsoft Word 2010 to make tables. Demographic data are given as mean with standard deviation (±SD) in parentheses if normal distributed, or median with percentiles if non-normal distributed. If satisfying normal distribution, differences between two measurements were analyzed by the Student's t-tests otherwise a non-parametric test were used. Analysis of Variance

(ANOVA, mixed models) was used to assess differences between three or more groups. Possible associations were assessed by the parametric Pearson's correlation coefficient (r). If r= > 0.7 then a strong correlation is found, while r=0.45-0.7 is considered as moderate and 0.2-0.45 is considered as weak. 0.0-0.2 represents no correlation (136). Probability value of p=0,05 or lower was used for all tests. The three groups are combined for more statistical power when analyzing possible associations between pulmonary function, BMI and body composition. To clarify which subjects who had the highest values regarding PF and DLco, the groups was also divided into additional sport groups in the analysis.

3.10 Ethical considerations

The present study was carried out according to scientific standards and will provide more information and intentionally contribute to increased knowledge about pulmonary function and the association with body composition in healthy and asthmatic athletes. The investigator will ensure that this study is conducted in full conformity with the principles set forth in the Declaration of Helsinki. The Regional Medical Ethics committee (REK) and the Norwegian data inspectorate have approved the study (Appendix in Norwegian).

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third part. None of the pulmonary measurements or the non-invasive measurement of body composition is considered to carry any element of risk. As subjects must refrain from any drugs before testing, the study may interfere with well-regulated anti-asthmatic treatment in some athletes. However, test days were facilitated to each subject's time schedule so that any competitions or training programs was not influenced by participation in the study and that there was no danger to the subject. Experienced health personnel were present during testing.

4.0 Results

4.1 Subject characteristics

Table 2: Subject characteristics with body composition for asthmatic athletes (group 1), healthy athletes (group 2), and healthy controls (group 3) (both genders)

Measure	Group 1 (n=25)	Group 2 (n=37)	Group 3 (n=27)
Age (year)	22,68 (±5,56)	18,92 (±3,12)	**27,15 (±5,34)** †#
Height (cm)	173,58 (±7,31)	178,09 (±10,19)	174,54 (±8,77)
Weight (kg)	67,70 (±10,97)	71,83 (±10,30)	72,71(±12,34)
BMI (kg/m^2)	22,36 (±2,43)	22,54 (±1,55)	23,66 (±2,41)
SMM (%)	48,03 (±3,39) ≠	48,89 (±4,61) ≠	**43,74 (±4,57)**≠ †#
FFM (%)	84,72 (±5,25)	86,82 (±5,78)	**78,25 (±6,87)** †#
FM (%)	15,28 (±5,22)	13,23 (±5,85)	**21,80 (±6,88)** †#
VFA (cm^2)	62,45(±26,05)	61,51 (±14,79)	66,21 (±26,67)

n=89. Values are means ±SD. † and advertised= significant compared to group 2 (p<0,05)
# and advertised= significant compared to group 1 (p<0,05)
≠=significant correlation (r) with FFM for all three groups (p<0,05)
BMI=body mass index, SMM=skeletal muscle mass, FFM=fat-free mass, FM=fat-mass, VFA=visceral fat area

The asthmatic athletes (group 1) consisted of 43,75 % males, the healthy athletes (group 2) of 64,28 % males, and controls (group 3) of 41,18 % males (Table 2). Group 1 was older than group 2 (p=,007) and group 3 was older than group 2 (p<,000), and group 1 (p=,002). Group 1 had higher SSM (p=,02) and FFM (p=,01) than group 3. Group 2 had higher SSM (p<,000) and FFM (p<,000) compared to group 3. Group 3 had higher FM compared to group 1 (p=,01) and group 2 (p<,000). When groups were combined and split by gender, males had higher SSM (p<,000) and FFM (p<,000) than the females, while females had higher FM (p<,000) compared to males.

FFM compared to SSM showed a perfect correlation (r= >,99) (Table 2).

4.2 Pulmonary function and diffusion capacity (DLco)

Table 3: Basic characteristics of selected measures of pulmonary function and DLco for asthmatic athletes (group 1), healthy athletes (group 2), and healthy controls (group 3) (both genders)

Measure	Group 1 (n=25)	Group 2 (n=37)	Group 3 (n=27)
FEV_1 % predicted	113,37 (±12,10)	**114,27(±15,10)**†	105,24 (±9,68)
FVC % predicted	119,98(±10,80)	117,33 (±15,26)	112,71 (±11,10)
MVV % predicted	137,53(±36,62)	**156,78(±42,56)**†	121,48 (±23,19)
TLC % predicted	101,18(±19,96)	103,18 (±16,47)	101,34 (±13,23)
DLco % predicted	107,00(±12,29)	**114,39(±16,41)**†	100,44 (±13,01)

n=89. Values are means ±SD. † and advertised=significant higher compared to group 3 ($p<0.05$)
FEV_1= forced expiratory volume in 1 s, FVC=forced vital capacity, FEF_{50}=forced expiratory flow 50 %, MVV = maximal voluntary ventilation, TLC= total lung capacity, DLco= diffusion capacity for CO

The results from the present study show significantly higher FEV_1 (p=,01) and MVV (p=,002) in group 2 compared to group 3 (Table 3). DLco were also significantly higher in group 2 compared to group 3 (p=,002). FEV_1, MVV, and DLco were not significantly different between group 1 and group 2, or between group 1 and group 3. No difference in FEV_1/FVC or FEF50 was found between the three groups in the present results. The males had higher DLco (p=,001) compared to females when all groups were combined.

4.3 Pulmonary function and diffusion capacity compared to body mass index and body composition

Only those values of PF as well as DLco which are found to be significantly different between the groups are presented in the next figures. Total lung capacity (TLC) was not found to correlate with BMI or body composition in the present results. The next figures are used to express how the main findings in Table 3 are associated with BMI, SSM, FM, and VFA.

4.3.1 Body mass index (BMI) compared to forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and diffusion capacity (DLco)

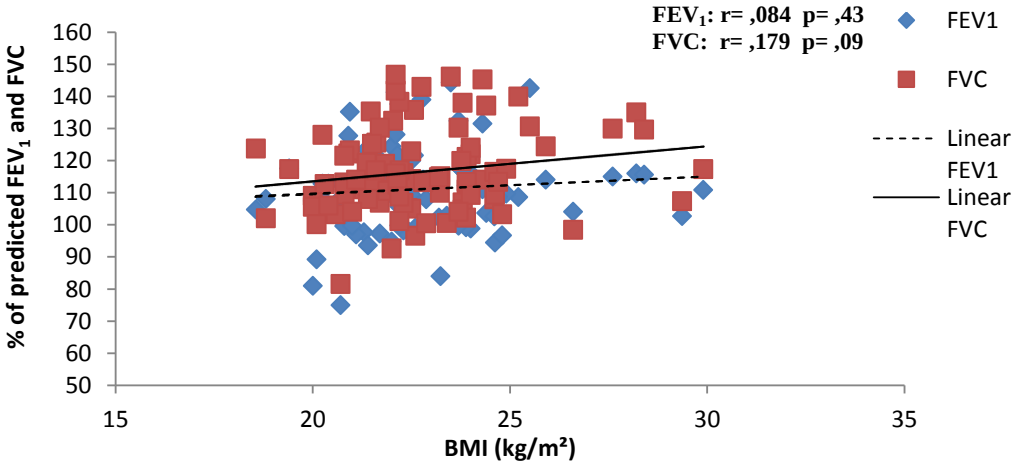


Figure 9: Correlation between forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) % pred. compared to body mass index (BMI) for asthmatic athletes (group1), healthy athletes (group2), and controls (group3), both genders. n=89.

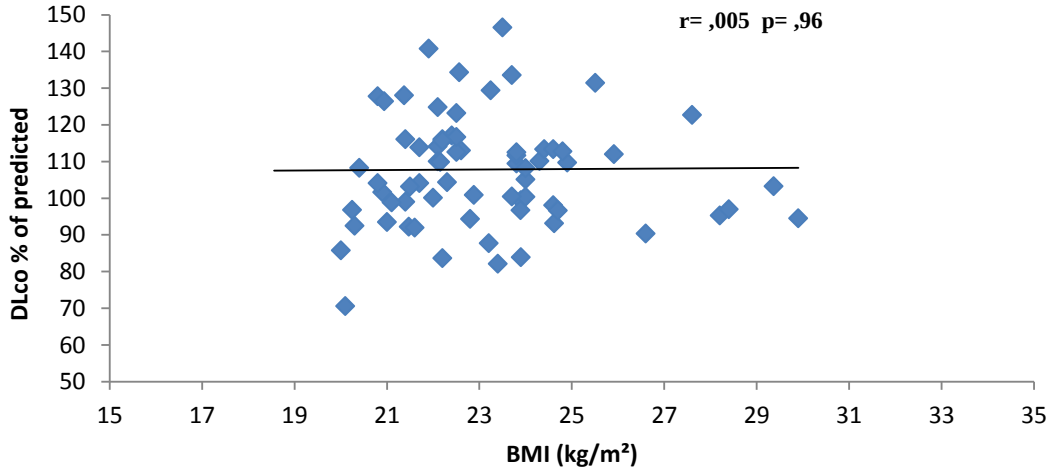


Figure 10: Correlation between diffusion capacity (DLco) % pred. compared to body mass index (BMI) for asthmatic athletes (group1), healthy athletes (group2), and controls (group3), both genders. n=71.

Weak correlations was observed between FEV_1 (L) (r= ,307 p= ,003) and FVC (L) (r= ,268 p= ,011) with BMI. FEV_1 and FVC (% pred.) (Figure 9) and DLco (% pred.) (Figure 10) shows however no association to BMI.

4.3.2 Skeletal muscle mass (SSM), fat-mass (FM), and visceral fat area (VFA) compared to forced expiratory volume in 1 s (FEV_1)

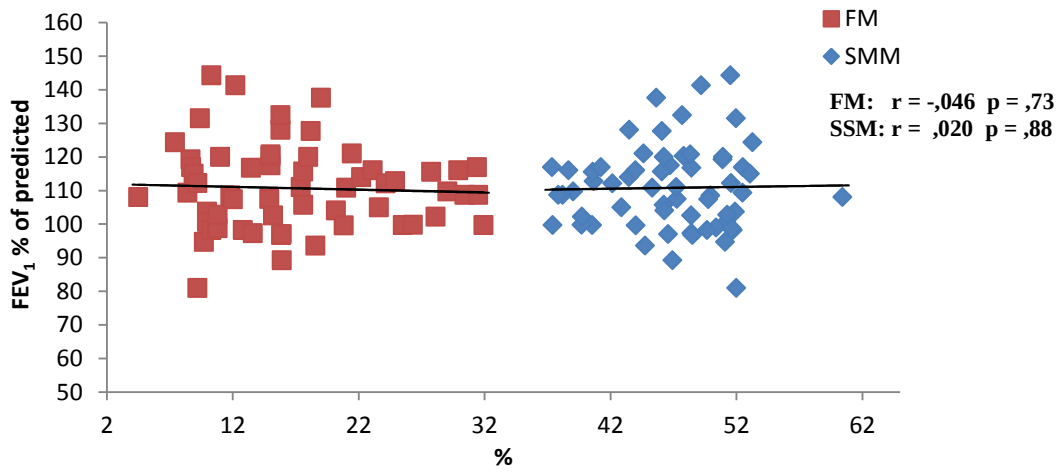


Figure 11: Correlation between forced expiratory volume in 1 s (FEV_1) % pred. compared to fat mass (FM) and skeletal muscle mass (SSM) (%of body weight) for asthmatic athletes (group1), healthy athletes (group2), and controls (group3), both genders. n= 60.

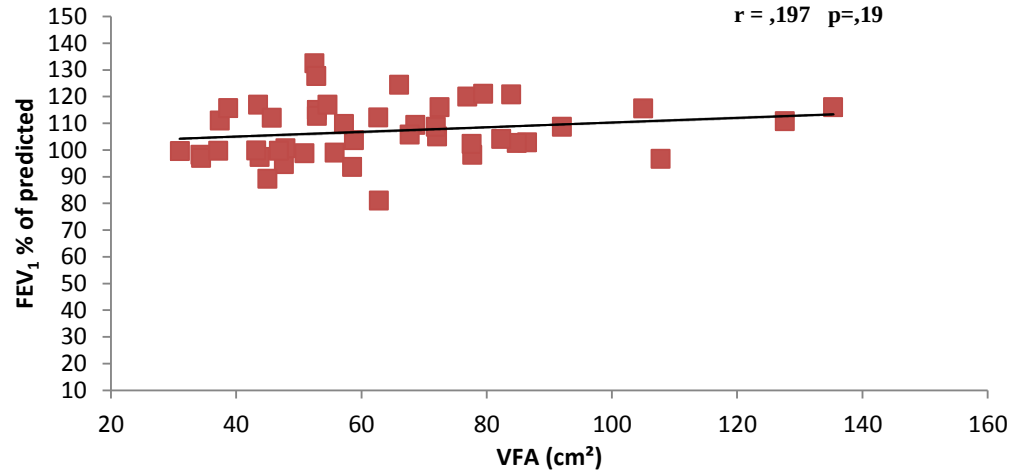


Figure 12: Correlation between forced expiratory volume in 1 s (FEV_1) % pred. compared to visceral fat area (VFA) (cm^2) for asthmatic athletes (group1), healthy athletes (group2), and controls (group3), both genders. n=45.

There are no correlations, neither between FM and FEV_1 % pred. (r=-,046) or between SSM and FEV_1 % pred. (r= ,020) (Figure 11). There are no correlation between VFA (cm^2) with FEV_1 % pred. (r =,197) (Figure 12).

4.3.3 Skeletal muscle mass (SSM), fat-mass (FM), and visceral fat area (VFA) compared to maximal voluntary volume (MVV)

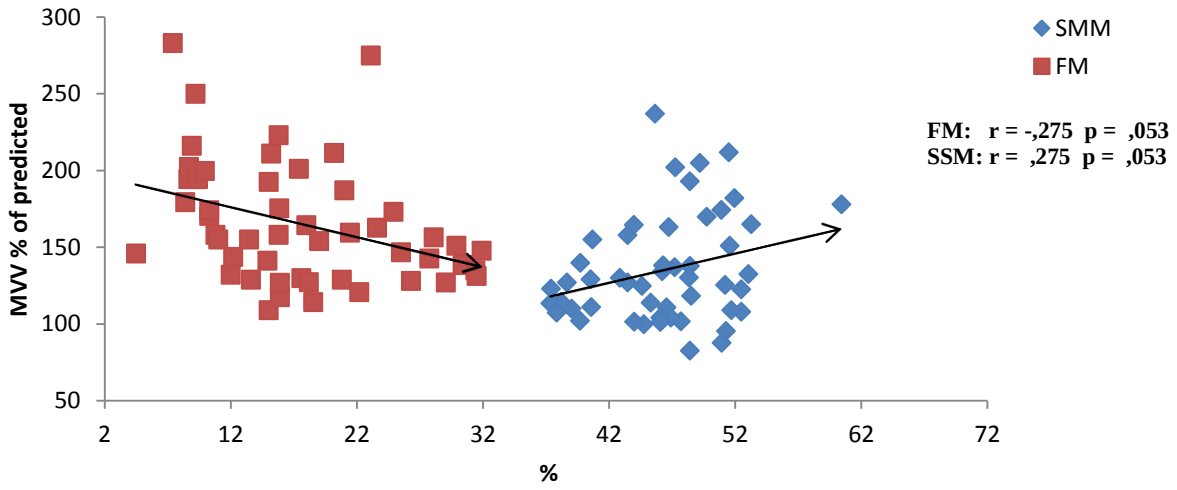


Figure 13: Correlation between maximal voluntary volume (MVV) % pred. compared to fat mass (FM) and skeletal muscle mass (SSM) (% of body weight) for asthmatic athletes (group 1), healthy athletes (group 2), and controls (group3), both genders. n=60.

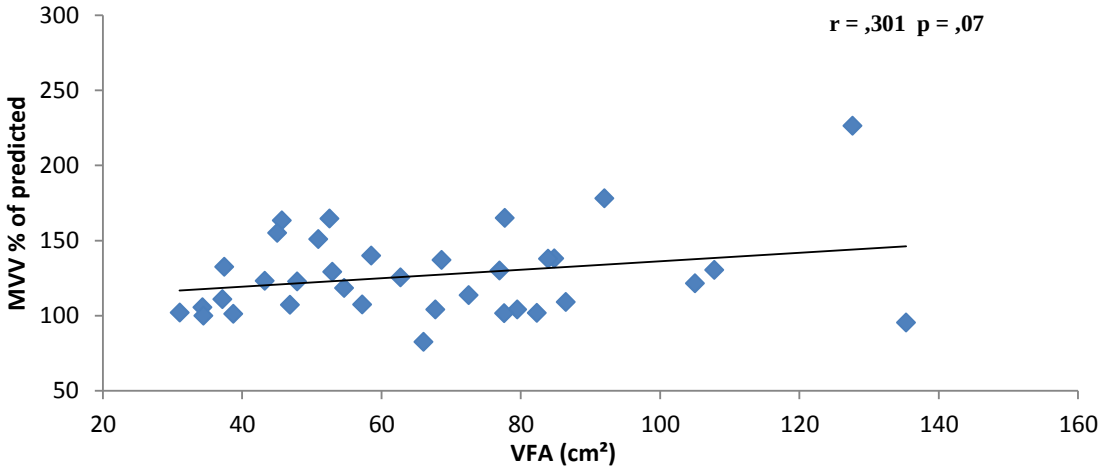


Figure 14: Correlation between maximal voluntary volume (MVV) % pred. compared to visceral fat area (VFA) (cm^2) for asthmatic athletes (group1), healthy athletes (group2), and controls (group3), both genders. n=45.

The correlation between MVV (% pred.) with FM is weak negative (r=-,275 p=,053) and weak positive with SSM (r=,275 p=,053) (Figure 13). The correlation between VFA (cm^2) and MVV (% pred.) is weak (r=,301), but not significant (Figure 14).

4.3.4 Skeletal muscle mass (SSM), fat-mass (FM), and visceral fat area (VFA) compared to diffusion capacity (DLco)

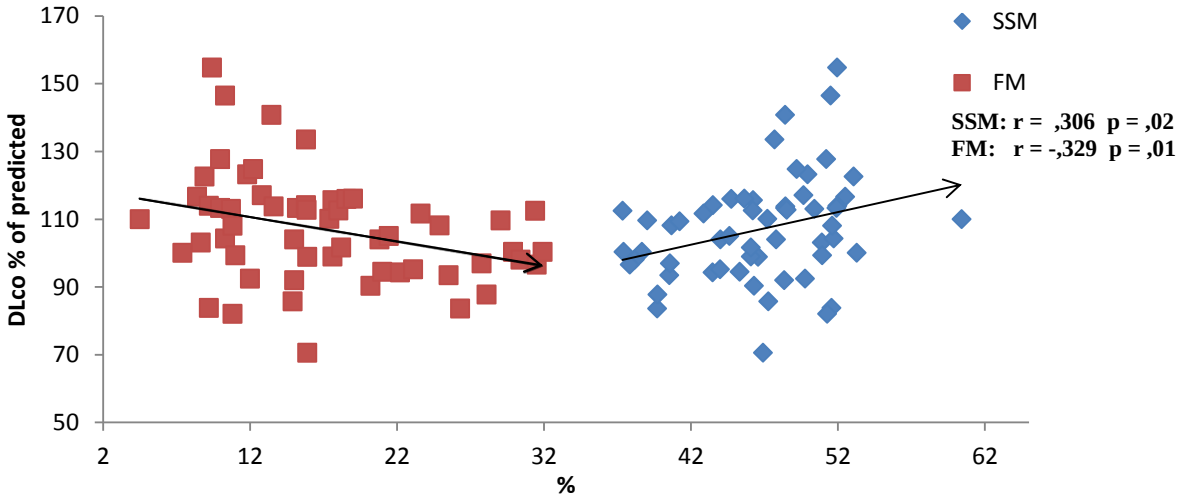


Figure 15: Correlation between diffusion capacity (DLco) % pred. compared to skeletal muscle mass (SSM) and fat mass (FM) (% of body weight) for asthmatic athletes (group1), healthy athletes (group2), and controls (group3), both genders. n= 60.

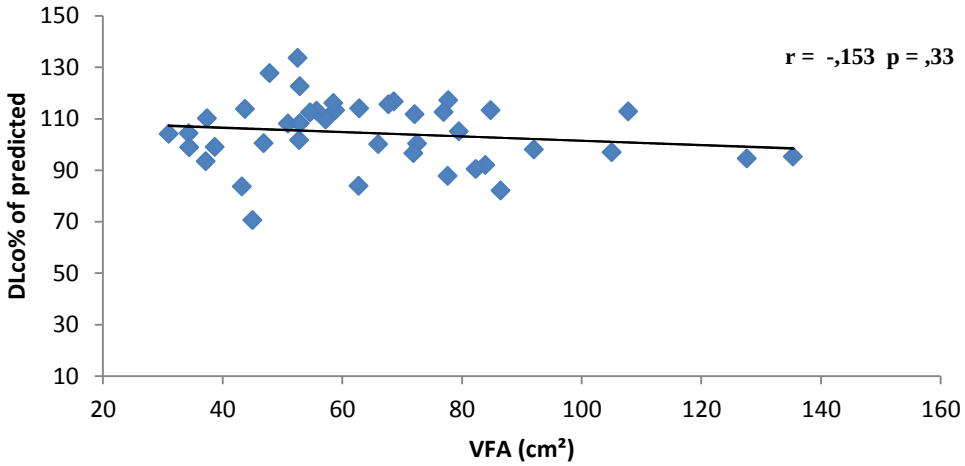


Figure 16: Correlation between diffusion capacity (DLco) %pred. compared to visceral fat area (VFA) (cm^2) for asthmatic athletes (group1), healthy athletes (group2), and controls (group3), both genders. n=42.

There is a weak negative correlation between FM and DLco (% pred.) (r=-,329 p=,01), but also a weak positive correlation between SSM (r=,306 p=,02) and DLco (% pred.) (Figure 15). The correlation between VFA (cm^2) and DLco (% pred.) is negligible (r= -,153) and not statistically significant (Figure 16).

4.4 Pulmonary function, lung volume, and diffusion capacity between swimmers, skiers, and controls

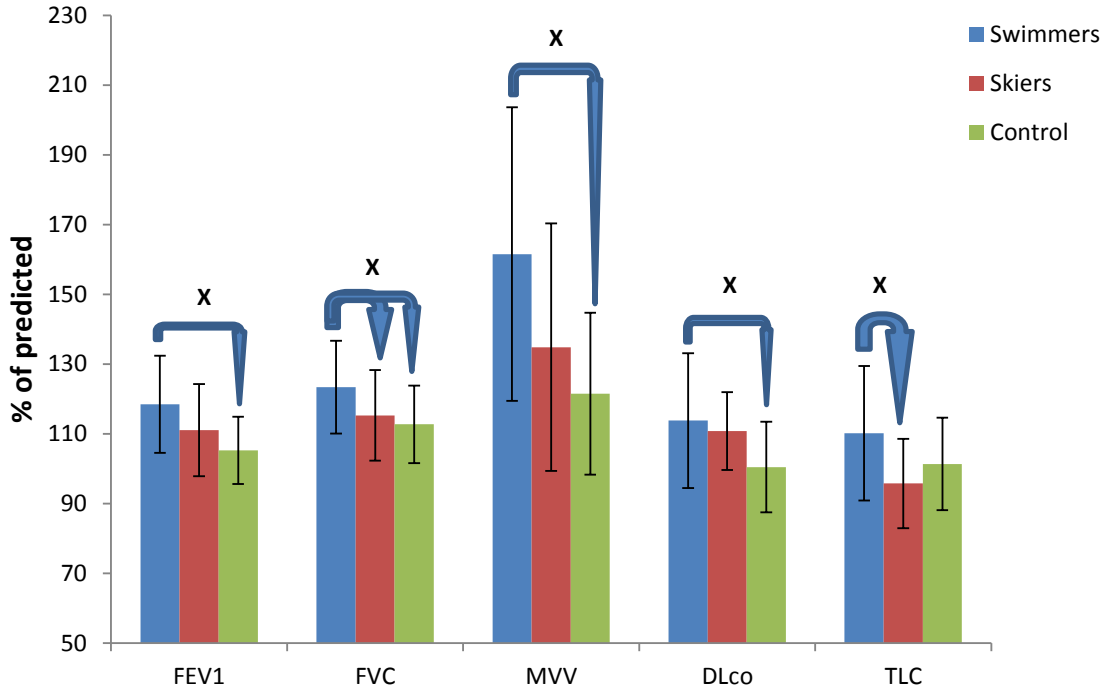


Figure 17: Pulmonary function; forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), maximal voluntary volume (MVV), lung volume; total lung capacity (TLC), and diffusion capacity (DLco) for 20 skiers and 5 swimmers in the asthmatic athlete group 1, 18 skiers and 19 swimmers in the healthy athlete group 2, and 27 healthy controls in group 3. both genders. n=89. Values are means±SD. X= significant difference between groups p<0.05

Female and male asthmatic and healthy swimmers, had significantly higher FEV_1 (p=,001), FVC (p=,01), MVV (p<,000), and DLco (p=,008) compared to controls (Figure 17). The swimmers had significantly higher TLC (p=,005) and borderline significantly (p=,052) higher MVV compared to female and male asthmatic and healthy skiers.

The swimmers had higher SSM (p=,006) and FFM (p=,002) compared to controls and higher VFA compared to the skiers (p=,02). The skiers had higher SSM (p=,001) and FFM (p<,000) compared to controls. Controls had higher FM compared to skiers (p<,000) and swimmers (p=,002). The swimmers were younger compare to the skiers (p=,003) and controls (p<,000). The skiers were younger than the controls (p<,000).

4.5 Pulmonary function, lung volume, and diffusion capacity between athletes with/without asthma and controls

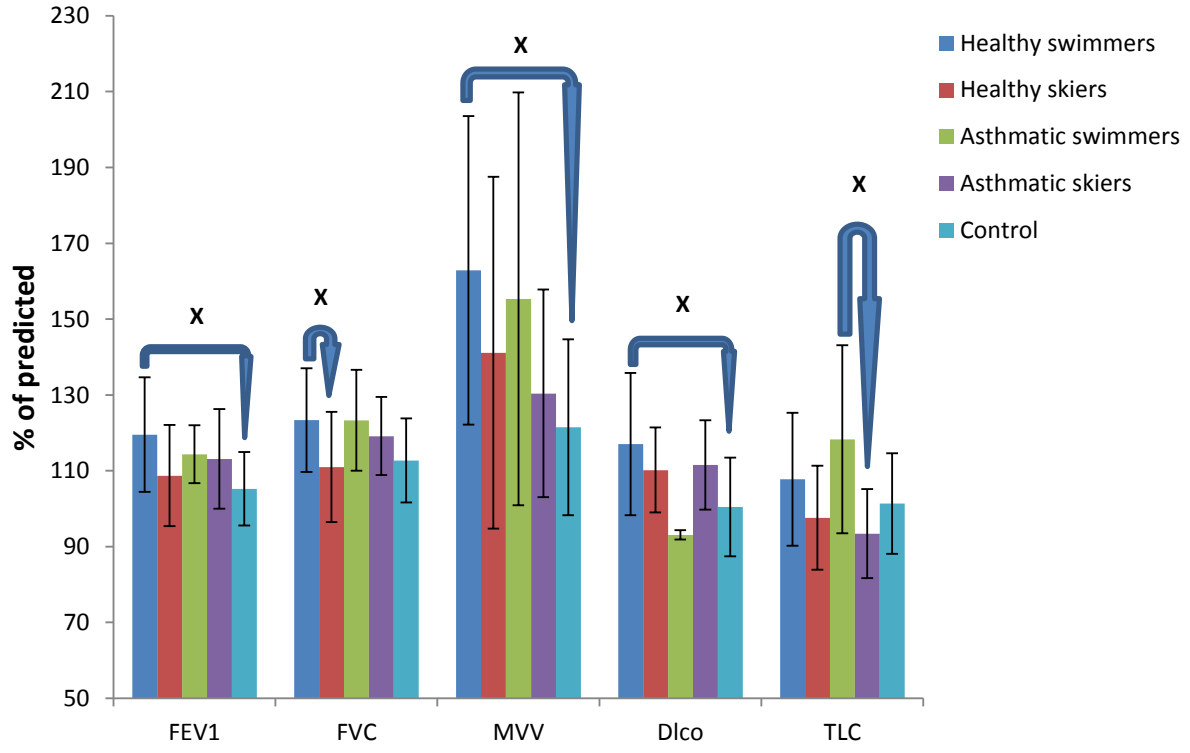


Figure 18: Pulmonary function; forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), maximal voluntary volume (MVV), lung volume; total lung capacity (TLC), and diffusion capacity (Dlco) between asthmatic athletes (group1), healthy athletes (group2), and controls (group3) divided by respective sport, both genders. n=89. X= significant differences between groups $p<0.05$. Values are means ±SD.

The present results shows that the healthy swimmers (n=19) had significantly higher FEV_1 (p=,003),) and MVV (p=,002) compared to controls (n=27). FVC (p=,03) were higher in the healthy swimmers compared to the healthy skiers (n=18). The healthy swimmers also tested higher DLco compared to controls (p=,002). The asthmatic swimmers (n=5) had higher TLC than the asthmatic skiers (n=20) (p=,03) (Figure 18).

The healthy swimmers had higher SSM (p=,02), higher FFM (p=,01), and were significantly younger (p<,000) compared to controls.

5. Discussion

5.1 Main findings

In the present study, pulmonary function (PF) is presented as FEV_1, FVC, FEV_1/FVC, FEF50, and MVV. Total lung volume is presented as TLC, while diffusion capacity is presented as DLco. FFM and SSM had a perfect correlation in the present study (Table 2), and therefore I have chosen to only include one of the variables in the analysis.

The results from the present study showed higher FEV_1, MVV, and DLco in the healthy athletes compared to controls (Table 3). No significant differences in PF variables or DLco were observed between asthmatic athletes and healthy athletes or controls. TLC was not found to be significantly different between the three groups (Table 3).

BMI was not found to correlate with PF, lung volume or DLco in the present study. The correlations between BC with PF and lung volume are scarce, although FM with MVV is weak negative and SSM with MVV is weak positive. The correlation is borderline significant (p=,053) (Figure 13). The results from the present study did however find a significant negative association between FM and DLco, and a positive association between SMM and DLco (Figure 15). These findings therefore suggest that increased FM may decrease MVV and DLco, while increased SSM may increase MVV and DLco. VFA did not correlate with FEV_1 (Figure 12), MVV (Figure 14), or DLco (Figure 16).

This is an observational case-control study, which do not follow the athletes and controls over time. Due to the study design, we cannot say that training increases PF, lung volume or DLco. However, the topic will be discussed to give possible explanations for the observed increased PF and DLco in the healthy athletes compared to healthy controls.

5.2 Asthmatic endurance athletes

5.2.1 Pulmonary function and lung volumes

In athletes with asthma, the PF are reported to be affected during periods of exercise in environments with allergens or pollution, such as cold air and organic chlorine in swimming pools (94). Rundell, Im & Schmitz (2001) found PF measured as FEV_1 at rest not to be different between 158 (male and female) Olympic athletes with and without self-reported EIA (9). This is in agreement with the present study (Table 3). This indicates that also asthmatic endurance athletes at national level have a normal FEV_1 at rest. FEV_1 at rest is also found to be within normal range in children with severe persistent asthma, aged between 5-18 years (137). FEV_1 correlated poorly with asthma symptoms in the same study (137). Baseline FEV_1 is found to poorly predict asthma in competitive athletes, since they often record PF values higher than the general population (138) which is supported by the present findings. One could assume that the well preserved FEV_1 in the self-reported asthmatic athletes in the present study are due to well-regulated anti-asthmatic treatment, increased muscle mass and/or exercise. Patients with other obstructive diseases like COPD are found to have an average FEV_1 (% pred.) as low as 48.0±18.3% (139). The asthmatic athletes in the present study had an average FEV_1 within normal range (113,37±12,10 % pred.) Results from the present study are in agreement with findings by Rundell et al., (2001), showing that FEV_1, FVC, and MVV are above 100 % pred. for both asthmatic swimmers and skiers (Figure 18). Asthma is characterized by airflow limitation (140). In the present study the subjects were tested only once. If tested again, there is a possibility that the asthmatic athletes would have tested lower FEV_1 compared to the healthy athletes. TLC was however below predicted values for the asthmatic skiers and significant lower compared to the asthmatic swimmers (Figure 18), although not below the lower clinical limit for TLC (80 % pred.) (1). When TLC is less than 80 percent, a restrictive pattern (problems with filling the lungs with air) is more likely rather than an obstructive pattern (1).

Fairshter, Carilli & Pai (1989) showed increased FEV_1 and MVV in healthy non-athletes compared to asthmatic non-athletes (141). The healthy athletes in the present study had significantly higher FEV_1 and MVV compared to controls. The asthmatic athletes showed no differences in FEV_1or MVV compared to controls. The results from the present study did not

show any differences in FVC or the FEV_1/FVC ratio between asthmatic athletes compared to healthy athletes and controls. FEV_1/FVC is often reduced in asthmatic subjects. FEV_1 is usually decreased while FVC is normal (within % pred.) in patients with obstructive diseases (1). Reduced FEV_1 and FEV_1/FVC ratio indicates an obstructive disease (1). The asthmatic athletes in the present study had an average FEV_1/FVC ratio of >0.8, which together with a normal FVC and FEV_1 indicates a normal spirometry (1). In addition, the result shows no decreased FEF50 in the asthmatic athletes compared to the healthy athletes and controls. This suggests no increased airway resistance in the asthmatic athletes compared to the healthy athletes and controls in the present study. A reduction of less than 60 (% pred.) would possibly have confirmed airway obstruction (1). The study by Fairshter et al., (1989) included asthmatic non-athletes with diagnosed asthma by a methacholine provocation. In the present study the subjects have been included based on asthma or not by a questionnaire. There is greater uncertainty with questionnaires compared to objective measures such as a metchacholine provocation.

5.3 Healthy endurance athletes

5.3.1 Pulmonary function and lung volumes

The present study supports earlier findings where increased FEV_1 was found in healthy runners compared to healthy sedentary controls (91). Although Prakesh, Meshram & Ramtekkar (2007) only included healthy males, we did not find FEV_1, FVC, FEV_1/FVC, MVV or TLC to be significantly different between genders in the present study. On the contrary, Vedala et al., (2013) found both increased FVC, FEV_1, and FEV_1/FVC (% pred.) in male and female Indian marathon runners compared to healthy sedentary subjects (44). Endurance exercise with regular forceful inspiration and expiration may lead to strengthening of the respiratory muscles and might increase the explosive capacity of the lungs. This might help the lungs to inflate and deflate maximally during forced expiratory maneuvers. This might be one explanation why athletes show higher FEV_1 and MVV in the present study.

The results from the present study contradicts to the study by Hagberg et al., (1988) who found no differences in FEV_1 or MVV between healthy young endurance athletes compared to age-matched sedentary controls (28), though the younger athletes had larger aerobic capacity and significantly lower FM compared to their age-matched sedentary controls. The older athletes in the study by Hagberg et al., (1988) had significant larger VC, TLC, and FEV_1 (% pred.) compared to the sedentary older subjects. The same study suggested that prolonged exercise for more than 10 years had decreased the age related deterioration in PF seen in older age. This might indicate that the observed difference in FEV_1 and MVV between healthy athletes and controls in the present study only will increase later in life. The possibility of a higher PF seen in older endurance athletes could be important and critical to know for sedentary subjects since VC is a strong predictor for cardiovascular mortality (142), and FEV_1 is a strong predictor of all-cause mortality (143).

5.4 Control group

It is important to state that even though differences were observed in PF between healthy athletes and controls in the present study, both groups had above average lower clinical limit (80 % pred.) of FEV_1 (Table 3) (1). The result from the present study shows higher MVV in the healthy athletes compared to the healthy controls. This may also be explained as poorer effort from the controls compared to the healthy athletes. The sedentary subjects in the study by Vedala et al., (2013) were less than 20 minutes PA/day. This is likely more sedentary than the control group in the present study. The control group in the present study reported to exercise as much as 5 hours/week. 5 hours PA or moderate exercise weekly is not considered as sedentary by national recommendations in Norway (8). The control group was recruited first and foremost from the Norwegian School of Sport Sciences. The control subjects are likely to be interested in PA and exercise and it is also likely that some were former endurance athletes. This might be one of the reasons why the results in the present study were different from the results reported by Prakesh et al., (2007) and Vedala et al., (2013).

5.5 Mechanical effects of body mass and body composition

5.5.1 FEV_1 and FVC

There were no significantly differences in weight or height between the groups in the present study (Table 2). No association between BMI and FEV_1 or FVC was found in the present study (Figure 9). This contradicts to results from a large population survey (80) and a cross-sectional study (52), which showed an inverse correlation between FEV_1 and FVC compared to BMI. There are also studies which found increased FEV_1 and FVC with increased BMI (68). Increased BMI is suggested to increase both FVC and FEV_1 until a certain point in younger subjects by the so called muscularity effect (67). Increased FEV_1, FVC, and lung volumes (TLC) are reported together with increased inspiratory muscle strength in healthy swimmers (27), which may suggest that the pulmonary system may be affected if the inspiratory muscles increase in strength. Findings on grip strength and it's positively association with FEV_1 and FVC (87) may suggest that strength is associated with stronger respiratory muscles (22, 88). The diaphragm has a similar structure and fatigue resistance as the skeletal muscles and exercise which are designed to improve skeletal muscle strength could also increase the respiratory muscle strength (31).

Additional weight, the so called adiposity effect, may be responsible for the observed decrease in FVC and FEV_1 (80). The effect of abdominal fat on the diaphragm, impeding the ability of the muscle to contract is a possible explanation for this (Figure 5). Lazarus et al., (1997) found BMI to be positively associated with the FEV_1/FVC ratio at all ages but negatively related to FVC between 40 and 69 years in healthy obese men (68). The same study also concluded that FEV_1 was decreased in men with high WHR. This is supported by a recent review article reporting decreased FVC and FEV_1 with increasing WHR (84), and a longitudinal study over 6 years, where weight gain significantly decreased FVC and FEV_1 in 709 adults (81).

In the present study we included endurance athletes. Investigating the effect of BMI and WHR on PF is off less value compared to Lazarus et al., (1997) who included obese subjects. Average BMI in the Norwegian population for 26-35 years old males and females combined are found to be 24.9±4.2 (8), not significantly different from the groups in the present study (Table 2). The influence of BMI was not investigated separately in group 1, 2, and 3. This is however unlikely to

be a confounding effect, knowing that no difference in BMI was observed between the groups (Table 2). BMI gives however little information about body composition.

In the present study, the athletes had higher SSM and FFM and lower FM compared to controls. This might be a possible explanation of the increased PF in the healthy athletes compared to controls. The respiratory muscles are important contributors during forced maneuvers which theoretically mean that subjects with greater respiratory muscle strength have greater FEV_1, FVC, and MVV. However, either FEV_1 or MVV were found to significantly correlate with SSM or FM. This is in agreement with Pekkarinen, Vanninen & Timonen (2012) who investigated the effect of muscle mass upon PF in healthy sedentary subjects (18). Karacan, Güzel & Baltaci (2008) found a positive association between FFM and FVC and FEV_1 (% pred.) in both men and women (52). A significant inverse correlation was demonstrated between increased BMI and FM compared to FVC for all subjects in the same study. The study by Karacan et al., (2008) included older non-athletes between (60-88 years), and measured fat mass and muscle mass by skinfold thickness. The skinfold thickness method highly depends on experienced test leaders who measure precisely the same site of the body each time (57). The use of BIA increases the validity compared to the skinfold-thickness method and measures BC more precisely. The athletes in the present study showed higher muscle mass and lower fat mass compared to the sedentary older subjects in the study by Karacan et al., (2008). Skinfold thickness may also overestimate FM. Mohamed, Maiolo & De Lorenzo (2002) showed that LBM (excluding the bone mass) adjusted for height with the use of DEXA correlated significantly with FVC (83). The association between LBM and FVC was stronger when adjusted for height compared to when adjusted for weight. SSM and FM in the present study are adjusted for weight. Measuring BC with different methods (skinfold-method, DEXA, BIA) together with different populations (athletes and sedentary) makes comparison of results difficult.

5.5.2 Maximal voluntary ventilation (MVV)

The borderline correlation found between SSM and FM with MVV in the present study (Figure 13) may indicate that subjects with high FM and low SSM would have decreased MVV compared to subjects with low FM and high SSM. The association may well have been stronger

with a larger sample of subjects with a wider range of FM and SSM. MVV (% pred.) is found to be within normal values in obese subjects (12, 144) and only below % pred. in severe obese subjects (12). Restrictive lung diseases (also caused by obesity) prevent the lungs to be fully filled with air. Increased abdominal fat may also decrease the ability to breathe rapid and deeply (89). The control group in the present study had higher FM compared to the healthy athletes (Table 2), which could be a possible explanation for the observed difference in MVV. Higher FM is however most unlikely an explanation, due to the non-obese subjects in the present study. Higher SSM in the healthy athletes compared to controls may on the other hand be a possible explanation. The respiratory muscles are recruited for vocalization and upright posture when performing different Valsalva-like maneuvers similar to the MVV maneuver (90). It is also a link between loss of FFM and loss of respiratory muscles mass (23). SSM may indirectly influence MVV as the respiratory muscles have an important role in active inspiration and greater respiratory muscles strength may also increase the forced expiration during MVV maneuvers. This might indicate that overweight patients with respiratory impairment should be encouraged to lose weight to improve their PF, since the present results indicates that FM has a negative association towards MVV even in normal weight subjects. Higher SSM may help the respiratory system to exhale greater amount of O_2 during forced maneuvers, which may be limited in obese subjects.

5.5.3 Diffusion capacity (DLco)

In healthy swimmers, increased DLco is found compared to predicted values (56, 95) and compared to non-athletes (11). This is in agreement with the findings in the present study (Figure 18). Yost, Zauner & Jaeger (1981) investigated DLco in healthy young children, comparing young swimmers to age, gender, and size matched non-athletes. The swimmers had significantly higher DLco (% pred.) compared to controls (11).

There was no significant association between BMI and DLco in the present study (Figure 10), which contradicts to the results from Pekkarinen et al., (2012). They found a weak positive association towards BMI and DLco in 284 non-obese healthy non-athletes. It is not unlikely that the present study also would have found a similar association with a larger sample of subjects,

and a wider specter of BMI (Table 2). Ray et al., (1983) reported significantly higher DLco (% pred.) in obese subjects with increased BMI, and decreased DLco after a period of weight loss (12). The present findings indicate however no association between BMI and to DLco.

In the present study, both higher SSM and FFM and higher DLco were found in the healthy athletes compared to controls (Table 3). These findings contradict to the findings from Ray et al., (1983). The swimmers (asthmatic and healthy) had higher SSM and FFM and DLco compared to controls (Figure 1). When the subjects were grouped into asthmatics or not, the healthy swimmers had both higher SSM and FFM and higher DLco compared to controls (Figure 18). DLco had a weak negative correlation to FM and a weak positive correlation to SSM in the present study (Figure 15). This is in agreement with Pekkarinen et al., (2012) who found a positive correlation between muscle mass and LBM compared to DLco (% pred.) (18). Increased muscle mass increases the blood volume (18). Increased pulmonary blood volumes are also found in swimmers (11). Higher pulmonary blood volumes are found together with increased DLco in swimmers after a period of swim training compared to swimmers without the same training period (27). The association between SSM and FM to DLco in the present results supports these findings. Athletes (with or without self-reported asthma) and controls with higher muscle mass had increased DLco, compared to those who had higher FM but lower muscle mass.

5.6 Methodological aspects

5.6.1 Study design

The present study is an observational case-control study, not controlled for genetic endowment or exercise. Concluding with causality between endurance training and superior PF or DLco is therefore not possible. Although the present study and previous findings clearly indicates that endurance athletes have superior PF and DLco, further research should include longitudinal studies, investigating the effects of genes and exercise upon PF, lung volumes and DLco. Further research should also investigate the development of muscle mass and fat-mass in athletes, and how it influences PF, lung volumes and DLco during growth in females and males separately.

5.6.2 Subjects

The present study included athletes based on self-reporting asthma/non asthma by a questionnaire. A questionnaire may well provide estimates of asthma and/or EIA prevalence. The possibility of high frequencies of both false positive and false negative outcomes are however likely to have occurred in the present study. Objective measurements compared to questionnaires had increased the reliability in the present study, given lower false positive and false negative outcomes.

Armour, Donnelly & Bye (1993) found increased lung volume and DLco in swimmers compared to significantly older sedentary subjects (56), which is in agreement with the results from the present study. PF, lung volumes and DLco (%pred.) are corrected for age, and should therefore not be affected by the fact that the healthy athletes were significant younger than the control group. The average age in the control group was 27,15 (±5,34), and are therefore unlikely to have influenced the results in the present study. FEV_1 is reported to decrease first at age 55-85 in non-athletic males and females (49). The differences in age between the groups are however a possible confounding factor.

The different group sizes may also be a confounding factor. PF and DLco are more likely to be significant higher in the healthy athletes (n=37) due to an increased number of subjects compared to the asthmatic athletes (n=25) and the controls (n=27). The healthy athletes also consisted of fewer females compared to the asthmatic athletes and control subjects. The gender difference is likely to have had an impact on the results in the present study. Though the present study did not investigate genders differences, the males had greater SSM, and the females had greater FM. DLco were significantly higher in males compared to females in the present study. A larger group of asthmatic athletes in the present study (Figure 18) may also have yielded out more statistical power.

5.6.3 Inbody 720

Inbody 720 used in the present study is not based on statistical data of any specific population as other BIA devices are. Although it is capable of accurately assess BC in people with very

different physical physique, Inbody 720 is sensitive to the subject hydration status. Subjects were asked if she/he had refrain from food and/or large amount of fluid ≤2 hours before testing. There was no standardized control if the subject was in a normal hydration status, which may have influenced the results, given higher or lower FM and/or FFM. DEXA is not as sensitive to the subject hydration status, and could have increased the reliability when measuring BC. However, the fact that Inbody 720 has showed an almost perfect correlation to DEXA, both for FFM in men (71) and FM in obese females (76) indicates its value in measuring BC. The test-retest conducted on Inbody720 in the present study showed a perfect correlation for SSM, FFM, FM, and VFA. Inbody 720 does not measure VFA in adolescents under the age of 18. Inbody 720 is found to be highly reliable to measure VFA in cancer patients compared to CT-scans (63). But in this case, the use of either DEXA or CT-scans probably would have increased the number of valid measurements of VFA. DEXA and CT-scans are however more time consuming and expensive compared to Inbody 720.

5.6.4 Measurement issues

The tests were performed by different test leaders, which is a limitation to the strength of the testing procedure and the inter-rater reliability. Though the test leaders were trained in the different measurements, this might have affected the results. Different test leaders may give different instructions and motivate the subjects differently. The learning effect can't be ruled out neither, since some subjects were familiar with the different measurements prior to testing. However, all tests were performed according to guidelines to minimize sources of error.

Athletes have increased total mass of red blood cells and higher Hb circulating compared to sedentary individuals (145). This is likely to have had an impact on the DLco results in the present study, since the amount of CO that diffuse into the blood is determined by the available quantity of Hb (40). This was not adjusted for in the present study. Although correction has only a very limited effect in healthy subjects with normal Hb levels (146), this is a possible confounding factor when investigating competitive endurance athletes.

5.7 Type of sport

Due to the present findings on the limited association between BC compared to PF, lung volume and DLco, some other mechanisms are needed to be investigated. Is type of sport related to the observed increased $FEV_{1,}$ MVV, and DLco, in the healthy athletes?

If all the swimmers were excluded from the present results no significant differences would have existed between the healthy athletes and the controls. The asthmatic and healthy swimmers combined had higher FEV_1, FVC, MVV, and DLco compared to controls, and higher FVC compared to skiers (Figure 17). Swimmers also had significant higher TLC and borderline significant (p=,052) higher MVV compared to skiers (Figure 17). The healthy athletes had an increased number of swimmers compared to the asthmatic athletes (Figure 17).

When the swimmers and skiers were grouped into being asthmatic or healthy, the results from the present study show that the healthy swimmers had significantly higher FEV_1, MVV and DLco compared to controls (Figure 18). The asthmatic swimmers in the present study did not show any significantly differences compared to controls, but a significantly higher TLC compared to asthmatic skiers (Figure 18). The results from the present study are in agreement with earlier studies from Doherty & Dimitriou (1997) which observed increased TLC and VC in healthy swimmers compared to healthy land-based athletes and healthy controls (10). Doherty & Dimitriou (1997) did however not include any asthmatic athletes. Armour et al., (1993) reported greater FVC and FEV_1 in the healthy swimmers compared to the significant older runners and age-matched controls (56). FVC in the present study was significant higher in healthy swimmers compared to healthy skiers (Figure 18).

5.8 Exercise or genetic endowment?

Increased PF after aerobic exercise is often explained by changes in BMI and/or increased muscle mass in healthy non-athletes (28, 46). It seems that it is prolonged exercise with high doses of swim training that may increase PF in healthy athletes (10, 54). It is not clear weather this is innate characteristics or due to the large amount of training. Eight weeks of aerobic exercise has shown to increase FEV_1 and FVC in asthmatic patients (147).

The increased lung volume and PF in swimmers (Figure 17) have largely been attributed to genetic endowment (148), although there are evidence that swim training itself may increase PF and lung volumes. Clanton, Dixon & Gadek (1987) tested PF and lung volumes before and after 12 weeks of high dosed swim training. They found increased lung volumes reported as VC, TLC, and FRC in 16 competitive female swimmers (54). This is in agreement with Zinman & Gaulder (1987) who found increased VC and TLC in 17 healthy female swimmers after one year follow up compared to age-matched controls (149). The question therefore arises why swimmers show higher PF and lung volumes compared to controls and to some extend land-based athletes. Ray et al., (1983) found increased TLC (% pred.) in subjects with increased DLco and suggested that increased lung volumes also leads to increased rather than decreased DLco. The results from the present study did not show significantly differences in TLC between the groups (Table 3) or in the swimmers compared to controls (Figure 17). The asthmatic swimmers showed however significantly higher TLC and decreased DLco compared to the asthmatic skiers (Figure 18). Although the difference in DLco was not significant it contradicts to the findings from Ray et al., (1983).

DLco and pulmonary capillary blood have been reported to remain unaltered in highly trained athletes, while the maximum pulmonary blood flow increases with enhanced VO_2 (150). However, the present study found increased DLco in healthy athletes compared to controls, first and foremost in swimmers. The explanation is likely due to the type of training the swimmers are performing. There is a large amount of upper body work in swimming, increasing the stress on the upper body muscles. Swimmers may also go repeatedly to TLC during swim training. This may lead to an increased ability to contract the inspiratory muscles, and may explain the increased TLC in swimmers observed in the present results (Figure 17). It has been suggested that high DLco in highly trained elite swimmers is due to the increased requirement of transferring large amounts of O_2 across the alveolar–capillary membrane when PaO_2 falls to low levels (151). Higher DLco may also be a consequence of an increased level of pulmonary capillary blood volume (95). Although it is unclear whether increased DLco is due to long term swim training or just an innate characteristic in swimmers, Armour et al. (1993) reported increased numbers of alveoli's together with increased DLco in highly competitive swimmers compared to long-distance runners and control subjects (56). Although the swimmers were younger, FFM and chest width were significantly greater compared to the long-distance runners

and controls. The latter makes room for larger lungs. Chest wide was found to significantly correlate with VC (56). The same study also found a significant association between FFM and VC in swimmers, but not in the group of runners or in the group of sedentary. The present results did not find any significantly correlations between FFM and SSM with forced maneuvers (FEV_1, FVC, and MVV).

There are observed increased lung volumes, diaphragm thickness, and increased swim performance after so called inspiratory muscle training (IMT) in people who are healthy and moderately trained (152, 153). Standard swim training is also shown to be equally as effective as IMT to increase PF (FVC, FEV_1), lung volumes (TLC), and DLco in young competitive swimmers (27). There was however no observed change in performance after IMT or swim training in the same study. The study by Miller et al., (1989) did not find any difference in swim performance between those athletes having higher DLco compared to those having lower DLco (% pred.). This supports the theory which says that the respiratory system of healthy young individuals usually is not considered a major limiting factor for high-intensity endurance exercise (154). An extremely high magnitude of stress put on the airways and chest wall during high intensity endurance training may lead to respiratory muscle fatigue. Respiratory muscle fatigue leads to hyperventilation which is shown to reduce cycling performance (155). However, healthy lungs perform their job of saturating the arterial blood with O_2 extremely well at sea level, even during maximal work (156). The lungs are overbuilt for the demands placed on ventilation and gas exchange during high-intensity short and long term exercise, and VO_{2max} is mainly limited by cardiac output and locomotor muscle blood flow (157).

5.9 Conclusion

In summary, results from the present study showed increased FEV_1, MVV, and DLco in healthy endurance athletes compared to controls. No differences were observed in pulmonary function, lung volume or DLco between asthmatic endurance athletes and healthy endurance athletes or asthmatic endurance athletes and controls. No differences were observed in TLC between the three groups. BMI was not associated with PF, lung volume or DLco in asthmatic and healthy endurance athletes and controls. SSM was associated with increased DLco, and FM was associated with decreased DLco in the present study.

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Appendixes

1. **Written informed consent from the "Masi-study" (in Norwegian)**
2. **Approval from the Regional Medical Ethics committee (REK) (in Norwegian)**
3. **Questionnaire (modified Aqua2008)**

Forespørsel om å delta i en forskningsstudie:
«Er toppidrett skadelig for luftveiene?»

Bakgrunn og hensikt
Forekomsten av astma har vist seg å være høyere blant idrettsutøvere enn hos personer som ikke driver idrett. Dette ser vi spesielt blant utøvere innen utholdenhetsidretter særlig utført i kulde eller i svømmehaller. Vi vet lite om årsakene til dette. Hensikten med studien er derfor å undersøke om systematisk utholdenhetstrening kan føre til skader på luftveiene som over tid kan lede til astma. Vi vil spesielt fokusere på sammenheng mellom høyintensiv trening og betennelsesprosesser i luftveiene, på nervesystemene i luftveiene og lungefunksjon.

Du blir forespurt om å delta fordi du er:
- **idrettsutøver innen utholdenhetsidrett med astma**
- **idrettsutøver innen utholdenhetsidrett uten astma**
- **er frisk og ikke driver konkurranseidrett (kontrollgruppe)**

Vi søker kvinner og menn i alderen 16-40 år. Idrettsutøvere må konkurrere på et høyt nasjonalt eller internasjonalt nivå og trene mer en 10 timer per uke. Kontrollgruppen kan ikke drive konkurranseidrett og må vanligvis trene mindre enn 5 timer per uke.

Hva innebærer studien?
Som forsøksperson vil du bli innkalt til to undersøkelser i løpet av tre uker på Norges idrettshøgskole (NIH) i Oslo. Hver undersøkelse vil vare mellom 1 og 2 timer og må foregå på separate dager med minimum 24 timer mellom.

Det vil bli utført medisinske undersøkelser inkludert lungefunksjonsundersøkelser, allergitest, måling av ulike betennelsesmarkører i utpust og oppsamlet sputum (slim) fra lungene, måling av pupillenes reaksjon på lys (pupillometri), en 4-sekunders anstrengelsestest og måle ømfintlighet i luftveiene. Vi vil også gjennomføre et intervju med spørsmål relatert til astma og allergi, og du vil fylle ut et spørreskjema. På dag 2 må du ta med en urinprøve og en prøve av spytt som du tar hjemme om morgenen, og vi vil ta en blodprøve. Undersøkelsene vil bli gjort av doktorgradsstipendiat Julie Stang i samarbeid med lege. Se **Kapittel A** for detaljert beskrivelse av undersøkelsene.

Mulige fordeler og ulemper
Det foreligger ingen umiddelbare fordeler for deg ved å delta, men du vil gjennomgå en grundig undersøkelse på lunge- og allergiske sykdommer. Målingene som utføres er ufarlige og medfører ingen spesiell risiko. Oppsamling av sputum kan være ubehagelig og medfører først en inhalasjon av astmamedisin etterfulgt av inhalasjon av saltvann som gjør at du hoster opp slim. Målingen av luftveienes ømfintlighet kan føre til en tung pust for en kort periode og du vil få astmamedisin etter testen. Noen få personer kan få en senreaksjon på med at de blir tungpustne noen timer etter testen. Dette forekommer ikke ofte, men dersom det skulle skje skal du kontakte prosjektet for å få videre behandling, om du ikke selv har astmamedisiner tilgjengelig. Det utbetales ingen godtgjørelse for studiedeltakelse, men reiseutgifter vil bli dekket etter statens satser for billigste reisevei.

Hva skjer med prøvene og informasjonen om deg?
Noen av prøvesvarene, som allergitesten og lungefunksjon, formidles direkte til deg på undersøkelsesdagen. Andre undersøkelser vil du ikke få svar på, fordi de vil bli analysert på laboratorier med høy vitenskapelig

kompetanse i Norge, Europa, USA eller andre land i henhold til det mest velegnede laboratoriet for den angjeldende analyse og inngår i forskning med usikker klinisk betydning for enkeltindivider. Informasjonen som registreres om deg er anonym og vil kun brukes slik som beskrevet i hensikten med studien.

Frivillig deltakelse
Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Det er frivillig å delta i studien og du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien.

Prosjektadministrasjon
Studien foregår i regi av OUS i samarbeid med Idrettsmedisinsk seksjon på Norges Idrettshøgskole (NIH). Ansvarlig for prosjektet er professor Kai-Håkon Carlsen ved OUS, Universitetet i Oslo og Norges idrettshøgskole.

Ytterligere informasjon om biobank, personvern og dine rettigheter finnes i Kapittel B

Har du spørsmål?
Kontaktpersoner:
Julie Stang, tlf: 23 26 24 01/98 41 14 40 eller epost: julie.stang@nih.no
Kai-Håkon Carlsen, tlf: 22 13 65 22 / 92 01 70 26 eller epost: k.h.carlsen@medisin.uio.no

Kapittel A: Utdypende forklaring for hva studien innebærer

Hvis du sier ja til å delta i studien, vil du få følgene informasjon fra oss:
- Brev om oppmøte og informasjon om undersøkelsene.
- På første undersøkelsesdag vil du få med deg et prøveglass hjem for å samle morgenurin. Dette tar du med til dag 2.
- Etter dag 2 vil du få et kort sammendrag av hva slags undersøkelse du har gjennomført og resultatene av disse undersøkelsene fra lege.

Undersøkelsene:
Når du kommer til undersøkelse kan du ikke ha vært syk de siste 3 ukene før (forkjølet, influensa, infeksjon el.). Dersom du er syk må vi utsette timen til det har gått 3 uker.

Du kan ikke være under påvirkning av luftveisutvidende medikamenter (bronkodilatorer) eller allergimedisiner. Dette betyr at følgene medikamenter skal ikke inntaes:

Samme dag	Inhalasjonspreparater av cortison: Pulmicort®, Flutide®, Aerobec®, Becotide®, Alvesco®, Astmanex®
8 timer før undersøkelse	Ventoline®, Salbuvent®, Inspiryl®, Bricanyl®, Airomir® og Lomudal til inhalasjon
12 timer før undersøkelse	Atrovent® til inhalasjon
3 døgn før undersøkelse	Serevent®, Seretide®, Oxis®, Symbicort®. Singulair® og Teophylline preparat (TheoDur®, Nuelin deport®)
7 døgn før undersøkelse	Antihistaminer: Phenamin®, Aereus®, Zyrtex®, Cetirizine®, Reactine®, Xyzal®, Clarityn®, Versal®, Loratadine®, Kestine®, Telfast®, Vallergan®

Oversikt over testdagene:

Dag 1. Ca 2 timer		**Dag 2. Ca 1.5 timer**
1. Ekshalert NO 2. Lungefunksjon 3. Allergitest 4. Intervju med spørreskjema 5. Pupillometri og 4sET 6. Blodprøve 7. EBC 8. Metakolin inhalasjonstest	**Min. 24 timer**	1. Spyttkortisol og urinprøve (tas hjemme og medbringes) 2. Ekshalert NO 3. Pupillometri og 4sET 4. Lungefunksjon 5. Lungevolum, diffusjonskapasitet 6. Indusert sputum

Hva som gjøres:

1. Ekshalert nitrogenoksyd (NO) måles ved at du fyller lungene med nitrogenfri luft fra et lite instrument, og deretter puster ut med en jevn luftstrøm i 10 sekunder. NO er en markør på grad av betennelse i nedre luftveier. Du vil gjennomføre 2-3 forsøk og hvert forsøk varer ca 20 sekunder.

2. Lungefunksjonen din måles ved at du trekker pusten så dypt du kan før du blåser ut hardt, fort og lenge gjennom et munnstykke. Du vil gjennomføre 2-3 forsøk og hvert forsøk varer ca 15 sekunder.

3. Det vil bli utført en prikktest for å vurdere allergi. De mest vanlige allergenene (pollen, dyrehår,muggsopp og husstøvmidd) er konsentrert i en liten dråpe saltvann (ca 12 ulike dråper) som legges på underarmen og prikkes så vidt under huden med en lansett. Testen tar ca 5 minutter og resultatet foreligger etter 15min.

4. Du vil bli bedt om å svare på et spørreskjema med spørsmål ang. astma og allergi.

5. Vi undersøker aktivitet i det parasympatiske nervesystemet ved å måle endringer i hjertefrekvens (HRV) ved bruk av en avansert pulsklokke under en svært kort sykkeløvelse på 4 sekunder (4s-ET). Under testen blir du bedt om å holde pusten i fire sekunder før du tråkker så raskt du kan i fire sekunder på en ergometersykkel. Vil vil også måle hvor raskt pupillen din trekker seg sammen etter lyseksponering. Dette kalles pupillometri og testen tar kun noen sekunder.

6. Blodprøve, urinprøve og spyttkortisol samles for å analysere på stoffer relatert til astma og allergi.

7. Vi vil samle opp kondensat fra luft du puster ut for analyse. Du skal da sitte i ro og puste helt normalt, inn gjennom nesen og ut i et munnstykke i 15 minutter. Denne målingen kan gi informasjon om betennelsestilstanden i luftveiene.

8. Du gjennomfører en metakolin inhalasjonstest for å bestemme ømfintligheten i luftveiene. Dette gjøres ved å måle lungefunksjonen før og etter inhalasjoner med metakolin i økende dose, inntil lungefunksjonen faller 20%. Avhengig av grad av reaktivitet vil testen ta mellom 5 og 20 minutter. Når du er ferdig får du en inhalasjon med astmamedisin (Ventoline®) for å åpne luftveiene helt igjen. Denne undersøkelsen kan gi en forbigående følelse av tetthet i brystet, men denne er svært lite uttalt. En lungefunksjonsmåling gjennomføres 15 min etter inhalasjon av astmamedisin.

9. På dag 2 vil vi måle lungevolumer ved helkroppsplethysmografi og diffusjonskapasitet (DL_{CO}) og motstand i luftveiene dine. Dette gjøres ved enkle pustetester hvor du blant annet holder pusten i 10 sekunder etter et maksimalt inn-pust, før du slipper luften rolig ut gjennom et munnstykke. Disse testene vil samlet ta ca. 15 minutter.

10. Det vil taes en prøve av slim fra luftveiene dine som produseres etter inhalasjon av hypertont saltvann. Dette kalles indusert sputum. Prosedyren går ut på at du «hoster» opp slim som vil bli analysert for innhold av inflammatoriske celler og epitelskade. Varighet på en slik prosedyre vil avhenge fra person til person, men vil være på mellom 20-45 minutter.

Kapittel B: Personvern, biobank, økonomi og forsikring

Personvern og frivillig deltakelse
All informasjon som samles inn i løpet av prosjektet er konfidensielle opplysninger som lagres forskriftmessig. Opplysninger og prøvesvar vil bli behandlet uten navn, fødselsnummer eller andre direkte gjenkjennende opplysninger ved at hver forsøksperson får et forsøksnummer. Koblingen mellom navn og forsøksnummer blir oppbevart i en lukket forskningsserver ved Oslo Universitetssykehus. Kun autorisert personell knyttet til prosjektet har innsyn i resultatene vedrørende den enkelte forsøksperson.

Hvis du trekker deg fra studien vil det ikke få noen konsekvenser for din videre behandling, eller forholdet til Oslo Universitetssykehus (OUS) eller Norges idrettshøgskole (NIH). Du har også rett til innsyn i data registrert om deg.

Sikkerhet
Undersøkelser som inngår i studien er vanlig benyttet klinisk praksis. Behandling for eventuelt respirasjonsbesvær vil kunne gis umiddelbart og det vil alltid være en erfaren lege tilstede ved undersøkelsene.

Etikk og biobank
Studien er vurdert av Regional Komité for medisinsk og helsefaglig forskningsetikk (REK)-Øst som ikke hadde innvendinger til studien. Hvis du sier ja til å delta i studien, gir du også samtykke til at det biologiske materialet og analyseresultater inngår i en forskningsbiobank ved OUS. Du gir du også ditt samtykke til at prøver kan utleveres til samarbeidende institusjoner for analyse, etter gjeldende retningslinjer og bli sendt til andre land, både i og utenfor Europa.Wenche Reed er ansvarshavende for biobanken, som planlegges å vare til 2028. Etter dette vil all informasjon bli anonymisert etter interne retningslinjer, dersom ikke endret samtykke foreligger.

Videre behandling av forsøksresultatene
Resultatene fra studien vil bli vitenskapelig behandlet og publiseres i internasjonale og nasjonale tidsskrifter og rapporter.

Rett til innsyn og sletting av opplysninger om barnet og sletting av prøver
Hvis du sier ja til at å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Økonomi
Studien og biobanken er finansiert gjennom forskningsmidler fra NIH og forskningsgruppen ORAACLE ved OUS. Studien er en del av et doktorgradsprosjekt ved NIH.

Forsikring
NIH er statlige institusjon og er derfor selvassurandør i forhold til studien.

Informasjon om utfallet av studien
Resultatene fra studien vil bli gjort offentlig tilgjengelig gjennom artikler og eventuelt rapporter. Det er planlagt å omtale studien i Allergi i Praksis som utgis av Norges Astma og Allergiforbund.

Samtykke/Consent

Jeg har lest informasjonsskrivet om Forespørsel om å delta i en forskningsstudie: «Er toppidrett skadelig for luftveiene?».

Jeg gir min tilslutning til deltagelse i undersøkelsen. Jeg er kjent med at jeg når som helst kan trekke meg fra prosjektet uten å måtte oppgi grunn for det. Jeg er klar over at de innsamlede data utelukkende brukes til forskning.

Forsøkspersonens navn: _____

Jeg nåes på telefon (dagtid): _____

Epostadresse: _____

Dato: _____ Underskrift: _____

For foresatte dersom forsøkspersonen er under 18 år:
Foresatte skriver under i tillegg til forsøkspersonen.

Dato: _____ Underskrift foresatte: _____

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Tor Even Svanes	22845521	07.03.2013	2013/167/REK sør-øst C
			Deres dato:	Deres referanse:
			22.01.2013	

Vår referanse må oppgis ved all henvendelser

Kai-Håkon Carlsen
Oslo Universitetssykehus

2013/167 Er toppidrett skadelig for luftvegene?

Forskningsansvarlig: Oslo Universitetssykehus
Prosjektleder: Kai-Håkon Carlsen

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 14.02.2013. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikkloven § 4.

Prosjektomtale
Forekomst av astma og bronkial hyperreaktivitet (BHR) er svært høy i kondisjonsidrett, særlig vinteridrett (langrenn, skiskyting) og svømming (>50% på landslagsnivå). Årsaken er ukjent Hensikten med studien er å klarlegge mekanismer for bedret forståelse som kan forebygge astma. Det vil være en case-kontroll studie der 30 toppidrettsutøvere med astma, 30 uten astma og 30 friske kontroller, i alderen 16-40 år, skal inkluderes. Man vil registrere lungefunksjon, BHR (metakolinprovokasjon)luftvegs-inflammasjon og -epitelskade (indusert sputum, ekshalert pustekondensat), prikktest, parasympatisk aktivitet (pupillometri og variasjon i cardialaktivitet)spyttkortisol, xenobioticaeksponering. Deretter skal man analysere sammenheng mellom faktorer og utvikling av astma og BHR Studien er samtykkebasert, og det vil opprettes en spesifikk forskningsbiobank.

Vurdering
Komiteen har ingen innvendinger til designet i studien.

Forskningsbiobank
Det søkes om å opprette en spesifikk forskningsbiobank med navn Er toppidrett skadelig for luftvegene? i prosjektet.

Ansvarshavende for forskningsbiobanken er Wenche Reed. Forskningsansvarlig er Oslo Universitetssykehus.

Biobanken vil bestå av blodprøver, urinprøver, spyttprøver, indusert sputum og luftveiskondensat.

Biobanken planlegges å vare til 2028. Deretter skal materialet behandles i henhold til helseforskningslovens § 30.

Biologisk materiale vil potensielt utføres til utlandet i henhold til helseforskningslovens § 37. Deltakerne er orientert om dette i informasjonsskriv.

Informasjonsskriv og samtykkeerklæring
Informasjonsskrivet er sterkt preget av fagterminologi og medisinske begreper. Skrivet er dessuten langt. Begge deler gjør informasjonen til deltakerne mindre tilgjengelig enn den hadde trengt å være. Det bes om at prosjektleder gjennomgår skrivet med tanke på å gjøre det mer allmenngyldig.

Det bes videre om at selve samtykkeerklæringen flyttes til etter kapittel A og B av skrivet. Samtykkeerklæringen skal komme etter at all relevant informasjon er gitt.

Endelig bes det om at det anføres at REK sør-øst har godkjent studien. I det foreliggende skrivet står det at REK har vurdert studien og ikke har innvendinger.

Ut fra dette setter komiteen følgende vilkår for prosjektet:

1. Informasjonsskriv skal revideres i tråd med det ovennevnte, og sendes komiteen til orientering.

Vedtak
Prosjektet godkjennes under forutsetning av at ovennevnte vilkår oppfylles, jf. helseforskningslovens §§ 9 og 33.

I tillegg til vilkår som fremgår av dette vedtaket, er tillatelsen gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden og protokollen, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Tillatelsen gjelder til 31.12.2018. Av dokumentasjons- og oppfølgingshensyn skal opplysningene likevel bevares inntil 31.12.2023. 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.

Komiteens avgjørelse var enstemmig.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK sør-øst på eget skjema senest 15.08.2016, 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. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse og omsorgssektoren.

Vi ber om at alle henvendelser sendes inn med korrekt skjema via vår saksportal: http://helseforskning.etikkom.no. Dersom det ikke finnes passende skjema kan henvendelsen rettes på e-post til: post@helseforskning.etikkom.no.

Med vennlig hilsen

Arvid Heiberg
prof. dr.med
leder REK sør-øst C

Tor Even Svanes
seniorrådgiver

3657

Patient ID ☐☐ - ☐☐☐

Centre ID ☐☐

Modified AQUA$_{2008}$

Questionnaire for assessment of asthma, allergy and other repiratory disorders for athletes participating in the Summer Olympic Games in Beijing August 2008

Country _____

Date of birth (Day Month Year) ☐☐.☐☐.☐☐☐☐

Age (years): ☐☐

Gender: ☐ Male ☐ Female

Weight (kg): ☐☐☐

Height (cm): ☐☐☐

Type of sport _____

Sports Association _____

Club _____

1. Have you previously participated in other types of sports on a competitive level? ☐ Yes ☐ No

1b. Which other kind of sport did you practice? _____

2. How many times a week do you exercise? ☐ 3 ☐ More than 3 ☐ Daily

3. Every training session usually lasts:
   - ☐ Less than 2 hours
   - ☐ 2-3 hours
   - ☐ More than 3 hours

4. Are you training mainly: ☐ Outdoor ☐ Indoor ☐ Both

5. Did any doctor diagnose you with any of these allergic diseases?
   - ☐ Asthma
   - ☐ Allergic rhinitis (Hayfever)
   - ☐ Allergic conjunctivitis (with eye symptoms)
   - ☐ Urticaria (hives)
   - ☐ Atopic eczema
   - ☐ Drug allergy
   - ☐ Food allergy
   - ☐ Insect venom allergy (bee, wasp)
   - ☐ Anaphylaxis (Allergic shock)

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Patient ID ☐☐ - ☐☐☐

6. Do you suspect that you suffer from allergy, independently of any medical diagnosis ? ☐ Yes ☐ No

7. Have you ever used anti-allergic or anti-asthma drugs ? ☐ Yes ☐ No

7b. If yes, which?
- ☐ Antihistamins
- ☐ Corticosteroids
- ☐ Bronchodilators
- ☐ Laukotrien antagonists (singulair)
- ☐ Allergy vaccines

8. Is there any allergic subject in your family? ☐ Yes ☐ No

8b. If yes, who?
- ☐ Mother
- ☐ Father
- ☐ Sibling(s) including half siblings
- ☐ Other relatives
- ☐ Children

9. Do you often have red eyes with tears and itching? ☐ Yes ☐ No

10. Do you often have runny, itchy nose (apart from colds): ☐ Yes ☐ No

11. Have you ever felt tightness in your chest and/or wheeze? ☐ Yes ☐ No

12. Have you ever had itchy skin eruptions? ☐ Yes ☐ No

13. Have you ever had severe allergic or anaphylactic reactions? ☐ Yes ☐ No

14. Have you ever had shortness of breath, cough and/or itching of the throat during or following exercise? ☐ Yes ☐ No

14b. If yes, you have more difficulties:
- ☐ At the beginning of the training session
- ☐ At the end of the training session
- ☐ During the whole training session

15. If you have suffered from any of the above, did these symptoms occur:
- ☐ Mainly outdoor
- ☐ Mainly indoor
- ☐ Indoor and outdoor equally
- ☐ Mainly in spring
- ☐ Mainly in cold or humid conditions
- ☐ All year around
- ☐ Independently of any environmental conditions

16. Have you ever had allergic reactions to foods? ☐ Yes ☐ No

16b. If yes, do you remember to which food? _____

17. Have you ever had allergic reactions to drugs? ☐ Yes ☐ No

17b. If yes, do you remember to which drug? _____

18. Do you know that some drugs for allergic and respiratory diseases are prohibited or under restrictions by the World Anti-Doping Agency (WADA)? ☐ Yes ☐ No

18b. If yes, tick which substances, you think are included in this category:

- ☐ Antihistamines
- ☐ Bronchodilators
- ☐ Vasoconstrictors
- ☐ Topical corticosteroids (Nasal inhalers, eye droplets, dermatological preparations)
- ☐ Inhaled corticosteroids
- ☐ Injected or oral corticosteroids

19a. Do you think that anti-allergic and/or respiratory drugs may:

☐ Reduce performance ☐ Improve performance ☐ Don't affect performance

19b. Do you think that anti-allergic and/or respiratory drugs may be in conflict with anti-doping regulations? ☐ Yes ☐ No

20. Have you used more than three courses of any of these drugs during the last year? ☐ Yes ☐ No

20.b.. If yes, tick which category of drugs you did use:

- ☐ Antibiotics
- ☐ Anti inflammatory drugs
- ☐ Pain reducing drugs
- ☐ Drugs for reducing fever
- ☐ Others, which....

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Patient ID

21. Have you used any other (except anti-asthma/anti-allergic) drug during the last week?

☐ Yes ☐ No

21 b. If yes, which drug? _____

22. Do you frequently suffer from upper respiratory infections (pharyngitis, colds, otitis media, tonsillitis, laryngitis) or fever?

☐ Yes ☐ No

22 b. If yes, are these infections more frequent during periods when you train more often than usual or during overtraining periods?

☐ Yes ☐ No

23. Have you suffered from recurrent labial herpes?

☐ Never
☐ 1-3 times
☐ More than 3 times

24. How many times during the last year were you unable to train because of infections?

☐ Never
☐ 1-3 times
☐ More than 3 times

25. If you have respiratory symptoms, which?

☐ Episodes of heavy breathing
☐ Wheeze
☐ Cough
☐ Phlegm, expectorate

26.Does this occur?

a. During exercise / training / competition: ☐ Yes ☐ No

b. During colds ☐ Yes ☐ No

c, After contact with animals, pollens, others: ☐ Yes ☐ No

27. With respiratory symptoms and dyspnoea related to exercise, when and how?

a. During maximum exercise ☐ Yes ☐ No

b. After the exercise: ☐ Yes ☐ No

c. In the afternoon, after training and/or competition: ☐ Yes ☐ No

28. When you have these respiratory symptoms?

a. Is it difficult to inhale ☐ Yes ☐ No

b. Is it difficult to exhale ☐ Yes ☐ No

c. Both: ☐ Yes ☐ No

29. Do the respiratory symptoms / dyspnoea occur?

☐ Outdoors
☐ Indoors
☐ Both outdoors and indoors

30. How often do you have heavy breathing?

☐ Daily
☐ Several times a week
☐ Weekly
☐ Monthly
☐ More rarely

31. Does your respiratory symptoms increase with simultaneously?

☐ Low temperatures, cold air inhaled
☐ Fog

32. Do the respiratory symptoms have impact on your sports performance? ☐ Yes ☐ No

33. Do you have symptoms from eyes or nose? ☐ Yes ☐ No

34 a. Do you smoke? ☐ Yes ☐ No

34 b. If yes, how many cigarettes a day?

☐ Less than 5
☐ 5-20
☐ More than 20

35. Do you use snus? ☐ Yes ☐ No

36. Do you use any foods supplements (vitamins, amino acids, creatine)? ☐ Yes ☐ No