Elisabeth Edvardsen

Cardiopulmonary Exercise Testing in Health and Disease
Cardiorespiratory Fitness in Adults in Norway and in Lung Cancer Patients undergoing Surgery

DISSERTATION FROM THE NORWEGIAN SCHOOL OF SPORT SCIENCES • 2015

"Those who do not make time for exercise, will eventually have to make time for illness"

The Earl of Derby, 1863
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Oslo, May 2015
Elisabeth Edvardsen
SAMMENDRAG PÅ NORSK

Introduksjon:
Maksimalt oksygenopptak ($\dot{V}$O$_{2\text{max}}$) benyttes for å kvantifisere et individs aerobe kapasitet og kardiorespiratorisk form, og regnes som hovedvariabelen ved gjennomføring av en klinisk arbeidsbelastningsundersøkelse (CPET). Det er imidlertid begrensede referanseverdier for både $\dot{V}$O$_{2\text{max}}$ og andre kardiorespiratoriske variabler som benyttes for å tolke undersøkelsen. Videre foreligger det lite kunnskap om ende-kriterier for vurdering av maksimal innsats ved bestemmelse av $\dot{V}$O$_{2\text{max}}$, spesielt hos kvinner og eldre.

$\dot{V}$O$_{2\text{max}}$ er svært sentral hos pasienter med ikke-småcellet lungekreft. Mange pasienter har i utgangspunktet en dårlig kardiorespiratorisk form med en lav $\dot{V}$O$_{2\text{peak}}$, og denne vil forverres ytterligere som følge av operasjon. En predikering av pasientens postoperative funksjonelle status (langefunksjon og $\dot{V}$O$_{2\text{peak}}$) benyttes derfor i de Europeiske retningslinjene for å vurdere om pasienten tåler operasjon. Nøyaktigheten av denne predikeringen er imidlertid lite undersøkt.

Etter lungekirurgi er det lite man kan gjøre for å bedre lungefunksjonen. Systematisk trening kan derfor være en viktig tilleggsbehandling for å forbedre kardiorespiratorisk form, daglig funksjon og livskvalitet hos pasienten. Imidlertid er kunnskap om hvordan pasienten takler hard trening og effekten av denne etter kirurgi tilnærmet fraværende.

Hensikten med studien var å:
1. Kartlegge kardiorespiratorisk respons under maksimalt arbeid på tredemølle hos en representativ norsk populasjon, bestående av kvinner og menn i alder 20 til 85 år.
2. Kartlegge ende-kriterier for å kunne vurdere om et individ har oppnådd en reell $\dot{V}$O$_{2\text{max}}$.
3. Evaluere effekten av lungekreftkirurgi med hensyn til kardiorespiratorisk form målt på tredemølle, samt undersøke validiteten mellem predikert $\dot{V}$O$_{2\text{peak}}$ og målt $\dot{V}$O$_{2\text{peak}}$.
4. Studere effekten av et høy-intensivt utholdenhets- og styrketreningsprogram med hensyn til $\dot{V}$O$_{2\text{peak}}$, langefunksjon, muskelstyrke, funksjonell form, kroppssammensetning og livskvalitet hos pasienter etter nylig gjennomgått lungekreftkirurgi.

Deltakere og metode
I 2008 gjennomgikk 3,485 personer fra hele Norge en objektiv måling av fysisk aktivitet i Kartleggingsstudien, KAN. Av disse møtte 904 deltakere opp til en helseundersøkelse for bl.a måling av kardiorespiratorisk form via en CPET på tredemølle. 759 deltakere fullførte CPET tilfredsstillende basert på definerte ende-kriterier (artikkkel I), og 859 deltakere fullførte CPET til frivillig utmattelse (artikkkel II). Videre gjennomgikk 70 pasienter med nylig påvist lungekreft målinger av lungefunksjon og CPET før operasjon og fire til seks uker etter operasjon. Endring i kardiorespiratorisk form ble vurdert, og den målte $\dot{V}$O$_{2\text{peak}}$ etter operasjon ble validert opp mot den estimerte $\dot{V}$O$_{2\text{peak}}$ mht nøyaktighet og presisjon (artikkkel III). Til sist ble 61 lungekreftpasienter randomisert til en treningsgruppe eller kontrollgruppe, hvor man undersøkte effekten av et høyintensivt utholdenhets- og styrketreningsprogram (60 min, tre
Hovedresultater og konklusjon
Artikkel I) $\dot{V}O_{2\text{max}}$ (mL·kg⁻¹·min⁻¹) var 40.3 ± 7.1 hos kvinnene og 48.6 ± 9.6 hos mennene i den yngste alderskohorten (20 til 29 år), og ble redusert med 8 % etter fylte 30 år hos begge kjønn per tiår. Maksimal hjertefrekvens ble redusert med 6.3 slag·min⁻¹ per tiår. Oksygenpulsen var 33 % lavere hos kvinnene, og ble redusert med 5 % og 3 % hos henholdsvis kvinner og menn per tiår. Kvinnenes maksimale minuttventilasjon var 66 % av mennenes, og ble redusert med alder etter 40 til 49 år hos begge kjønn. Pustereserven var høyere hos kvinnene enn hos mennene (henholdsvis 30 ± 13.7 % vs 23 ± 12.8 %, $P < 0.001$). Nye referanseverdier for maksimal CPET utført på tredemølle ble presentert i aldersgruppen 20 til 85 år.

Artikkel II) Maksimal blodlaktatkonsentrasjon og respiratorisk utvekslingsratio (RER) ble redusert med økende alder, til tross for at deltakernes subjektive grad av utmattelse (BORG skala) forble uendret. En valgt blodlaktat konsentrasjon ≥ 8 eller ≥ 6 mmol∙L⁻¹ og/eller RER ≥ 1.15 som kriterium for maksimal innsats under CPET gav en høyere $\dot{V}O_{2\text{max}}$, men utelukket et betydelig antall deltakere fra analysen. Nye anbefalinger for maksimal innsats ble gitt i henhold til alder og kjønn.

Artikkel III) Hos lungekreftpasientene var $\dot{V}O_{2\text{peak}}$ 23.9 ± 5.8 mL·kg⁻¹·min⁻¹ (80.6 ± 16.7 % av forventet) før operasjon, og ble redusert til 19.2 ± 5.5 mL·kg⁻¹·min⁻¹ ($P < 0.001$) etter operasjon. Oksygenpulsen var den sterkeste prediktor for endring i $\dot{V}O_{2\text{peak}}$: $r^2=0.77$. Seks måneder etter operasjon forble $\dot{V}O_{2\text{peak}}$ uendret (-3 ± 15 %, $P = 0.27$). Predikering av postoperativ $\dot{V}O_{2\text{peak}}$ basert på antall resekterte lungesegmenter viste lav presisjon i forhold til reell $\dot{V}O_{2\text{peak}}$.

Artikkel IV) Pasientene som deltok i treningsgruppen etter operasjon for lungekreft hadde signifikant større økning i $\dot{V}O_{2\text{peak}}$ (18.9 %), diffusjonskapasitet for karbonmonoksid i lungene (5.2 %), 1RM i bein press (23 %), funksjonell funksjon og livskvalitet, sammenliknet med pasientene i kontrollgruppen. Høy-intensiv utholdenhet og styrketrening var godt tolerert untatt under pågående kjemoterapibehandling.
SUMMARY

Introduction:
Maximal oxygen uptake ($\dot{V}O_{2\text{max}}$) is used to quantify an individual’s exercise capacity and is recognized as the main variable for measurement during cardiopulmonary exercise testing (CPET). There are limited reference values for $\dot{V}O_{2\text{max}}$ and other cardiorespiratory fitness variables measured during CPET. There are also few typical criteria for ascertaining that the subject has achieved the maximum effort needed to ensure a valid measurement, especially among women and elderly people.

In patients with Non-Small-Cell lung cancer (NSCLC), $\dot{V}O_{2\text{max}}$ is a cornerstone in the preoperative evaluation. Many patients have poor physical fitness, which may decline further after surgery. The accuracy of the predicted postoperative functional outcome (pulmonary function and $\dot{V}O_{2\text{max}}$) recommended in the European risk assessment guidelines has not been investigated thoroughly. After lung surgery, there is little that can be done to improve lung function and the area for gas exchange, and exercise training may be the single most important aspect of adjuvant treatment to increase daily function and quality of life. However, knowledge about the feasibility and effects of training after lung resection is limited.

The overall objectives of this thesis were to:

1. Determine the cardiorespiratory response during maximal treadmill exercise in a well-described representative sample of 20-to 85-year-old men and women in Norway.
2. Identify the end criteria for determining that a subject has reached $\dot{V}O_{2\text{max}}$.
3. Evaluate the effect of lung cancer surgery on cardiorespiratory fitness measured on a treadmill, and to assess the agreement between the predicted postoperative peak oxygen uptake ($\dot{V}O_{2\text{peak}}$) and actually measured postoperative $\dot{V}O_{2\text{peak}}$.
4. Study the effect of high-intensity endurance and strength training on $\dot{V}O_{2\text{peak}}$, pulmonary function, muscular strength, functional fitness, body composition, and quality of life in a randomised controlled trial of newly resected NSCLC patients.

Participants and methods:
In 2008, 3,485 individuals from all parts of Norway underwent objective measurement of physical activity in the KAN1 study. From this sample, a total of 904 men and women undertook a CPET; 759 successfully completed a maximal treadmill exercise test based on defined maximum end criteria (paper I), and 859 participants completed the test until voluntary exhaustion (paper II). Furthermore, 70 NSCLC patients completed measurement of pulmonary function and CPET before and 4–6 weeks after surgery. In these patients, the changes in cardiorespiratory fitness were evaluated and were used to predict...
postoperative $\dot{V}O_{2\text{peak}}$ (paper III). Finally, 61 lung cancer patients were randomised into a training or control group, and the effect of high-intensity endurance and strength training were assessed (60 min, three times a week, 20 weeks) (paper IV). The primary outcome was the change in $\dot{V}O_{2\text{peak}}$. Other outcomes included changes in pulmonary function, muscular strength, functional fitness, total muscle mass, and quality of life.

**Main results and conclusions**

**Paper I** In the 20- to 29-year old age group, $\dot{V}O_{2\text{max}}$ (mL·kg$^{-1}$·min$^{-1}$) was 40.3 ± 7.1 in women and 48.6 ± 9.6 in men. A linear decline (8 % per decade) was observed after age 30 years in both sexes. Maximal heart rate decreased with age by 6.3 beats·min$^{-1}$ per decade. The maximal $O_2$ pulse was 33 % lower in women and decreased with age by 5 % and 3 % per decade for women and men, respectively. Women’s maximal ventilation was 66 % that of men and decreased with age after 40 to 49 years in both sexes. Breathing reserve was higher in women than in men, (30 ± 13.7 % vs 23 ± 12.8 %, respectively, $P < 0.001$). New reference values for maximum CPET on a treadmill were derived for ages 20 to 85 years.

**Paper II** Post exercise blood lactate concentration and the respiratory exchange ratio (RER) decreased with age, even though the subjective ratings of exertion related to age remained unchanged. Choosing a blood lactate concentration of $\geq 8.0$ or $\geq 6$ mmol·L$^{-1}$ and/or RER $\geq 1.15$ to indicate a maximum effort yielded a higher $\dot{V}O_{2\text{max}}$ but excluded a significant number of participants from the analysis. Suggestions for new recommendations for end criteria were given according to age and sex.

**Paper III** The average $\dot{V}O_{2\text{peak}}$ in lung cancer patients was 23.9 ± 5.8 mL·kg$^{-1}$·min$^{-1}$ (80.6 ± 16.7 % predicted) before surgery, and decreased to 19.2 ± 5.5 mL·kg$^{-1}$·min$^{-1}$ ($P < 0.001$) after surgery. The $O_2$ pulse was the strongest predictor for change in $\dot{V}O_{2\text{peak}}$, adjusted linear squared $r^2 = 0.77$. Six months after surgery, the $\dot{V}O_{2\text{peak}}$ remained unchanged (-3 ± 15 %, $P = 0.27$). Predicting postoperative $\dot{V}O_{2\text{peak}}$ based on the number of lung segments removed showed poor precision when compared with actually measured postoperative $\dot{V}O_{2\text{peak}}$.

**Paper IV** After lung cancer resection, the patients in the exercise group who completed the supervised high-intensity endurance and strength training program had significantly larger increases in VO$2_{\text{peak}}$ (18.9 %), diffusion capacity of the lung for carbon monoxide (5.2 %), 1RM in leg press (23 %), functional fitness, and quality of life compared with the controls. High-intensity endurance and strength training was well tolerated except during chemotherapy.

**Key words**: Cardiorespiratory fitness, cardiopulmonary exercise testing, maximal oxygen uptake, peak oxygen uptake, normal response, blood lactate concentration, respiratory exchange ratio, non-small-cell lung cancer, surgery, predicted postoperative function, high-intensity exercise training, randomised controlled trial.
LIST OF PAPERS

The dissertation is based on the following original research papers:


II. Edvardsen E, Hem E, Anderssen SA. *End Criteria for reaching Maximal Oxygen Uptake must be Strict and Adjusted to Sex and Age*. Plos One; 2014, 9 (1), e85276

III. Edvardsen E, Anderssen SA, Borchsenius F, Skjånsberg OH. *Reduction in Cardiorespiratory Fitness after Lung Cancer Surgery is not related to Amount of Lung Tissue Removed*. In manuscript.

IV. Edvardsen E, Skjånsberg OH, Holme IM, Nordsletten L, Borchsenius F, Anderssen SA. *High-Intensity Training following Lung Cancer Surgery — A Randomised Controlled Trial*. Thorax; 2014, 70 (3), 244-250

The papers are referred to by their Roman numeral throughout the thesis.
ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C&lt;sub&gt;a&lt;/sub&gt;-C&lt;sub&gt;v&lt;/sub&gt;) O&lt;sub&gt;2&lt;/sub&gt; difference</td>
<td>Arteriovenous oxygen difference</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BTS</td>
<td>British Thoracic Society</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure (mmHg)</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CPET</td>
<td>Cardiopulmonary exercise test</td>
</tr>
<tr>
<td>CPM</td>
<td>Counts per minute</td>
</tr>
<tr>
<td>CRF</td>
<td>Cardiorespiratory fitness</td>
</tr>
<tr>
<td>DLCO</td>
<td>Diffusion capacity of the lung for carbon monoxide (mmol-kPa&lt;sup&gt;-1&lt;/sup&gt;∙min&lt;sup&gt;-1&lt;/sup&gt;)</td>
</tr>
<tr>
<td>DO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Oxygen-delivery capacity</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>ERS</td>
<td>European Respiratory Society</td>
</tr>
<tr>
<td>ESTS</td>
<td>European Society for Thoracic Surgery</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Forced expiratory volume after 1 second (L)</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity (L)</td>
</tr>
<tr>
<td>FFM</td>
<td>Fat free mass</td>
</tr>
<tr>
<td>[Hb]</td>
<td>Haemoglobin concentration</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate (beat∙min&lt;sup&gt;-1&lt;/sup&gt;)</td>
</tr>
<tr>
<td>[La&lt;sub&gt;-&lt;/sub&gt;]</td>
<td>Blood lactate concentration</td>
</tr>
<tr>
<td>MET</td>
<td>Metabolic equivalent, equal to 3,5 mL oxygen per body weight per min</td>
</tr>
<tr>
<td>MVPA</td>
<td>Moderate to vigorous intensity physical activity</td>
</tr>
<tr>
<td>MVV</td>
<td>Maximal voluntary ventilation (L∙min&lt;sup&gt;-1&lt;/sup&gt;)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Non-Small-Cell lung cancer</td>
</tr>
<tr>
<td>O&lt;sub&gt;2&lt;/sub&gt;-pulse</td>
<td>Oxygen pulse (mL∙beat&lt;sup&gt;-1&lt;/sup&gt;)</td>
</tr>
<tr>
<td>PRT</td>
<td>Progressive resistance training</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trials</td>
</tr>
<tr>
<td>RER</td>
<td>Respiratory exchange ratio</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SpO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Oxygen saturation measured by pulse oximeter (%)</td>
</tr>
<tr>
<td>V&lt;sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;&lt;/sub&gt;</td>
<td>Carbon dioxide output</td>
</tr>
<tr>
<td>V&lt;sub&gt;E&lt;/sub&gt;</td>
<td>Minute ventilation (L∙min&lt;sup&gt;-1&lt;/sup&gt;)</td>
</tr>
<tr>
<td>V&lt;sub&gt;E&lt;/sub&gt;/VCO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Ventilatory equivalent for V&lt;sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;&lt;/sub&gt;</td>
</tr>
<tr>
<td>V&lt;sub&gt;O&lt;sub&gt;2&lt;/sub&gt;&lt;/sub&gt;</td>
<td>Oxygen uptake (mL∙kg&lt;sup&gt;-1&lt;/sup&gt;∙min&lt;sup&gt;-1&lt;/sup&gt; or L∙min&lt;sup&gt;-1&lt;/sup&gt;)</td>
</tr>
<tr>
<td>V&lt;sub&gt;O&lt;sub&gt;2max&lt;/sub&gt;&lt;/sub&gt;</td>
<td>Maximal oxygen uptake</td>
</tr>
<tr>
<td>V&lt;sub&gt;O&lt;sub&gt;2peak&lt;/sub&gt;&lt;/sub&gt;</td>
<td>Peak oxygen uptake, used when defined criteria for maximum effort is not fulfilled</td>
</tr>
<tr>
<td>Q&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximal cardiac output</td>
</tr>
</tbody>
</table>
1.0 INTRODUCTION

In general, maximal oxygen uptake ($\dot{V}O_{2\text{max}}$) has been shown to be an excellent predictor for mortality and long-term survival, and is recognized as the gold standard variable measured during cardiopulmonary exercise testing (CPET). There are limited reference values for $\dot{V}O_{2\text{max}}$ and other cardiorespiratory fitness variables used in the clinical settings. In addition, agreement about the end criteria for determining that a subject has achieved a maximum effort to ensure a valid $\dot{V}O_{2\text{max}}$ is lacking, and current guidelines do not take into account age and sex differences.

Maximal or peak oxygen uptake ($\dot{V}O_{2\text{peak}}$) is also an important variable in patients with Non-Small-Cell lung cancer (NSCLC). Many patients have poor cardiorespiratory fitness and a low $\dot{V}O_{2\text{peak}}$, which may be a contraindication for life-saving surgical treatment. $\dot{V}O_{2\text{peak}}$ declines significantly after lung resection in most patients, although the extent of and reason for this decline are unclear. After surgery, the loss of lung tissue is irreversible, and there is little that can be done to improve lung function and the area for gas exchange. Thus, exercise training may be the single most important factor for recovering some of the lost cardiorespiratory fitness needed to restore physical function and quality of life after surgery.

The first part of this thesis suggests a new set of reference values for CPET and new recommended criteria for determining that the subject has achieved maximum effort. The second part of the thesis investigates the changes in cardiorespiratory fitness early in the recovery from NSCLC surgery, predictors of postoperative functional outcomes (e.g., pulmonary function and $\dot{V}O_{2\text{peak}}$), and studied the effects of high-intensity endurance and strength training on $\dot{V}O_{2\text{peak}}$, pulmonary function, muscular strength, total muscle mass, functional fitness, and quality of life after lung cancer surgery.
2.0 GENERAL BACKGROUND INFORMATION

2.1 Cardiopulmonary exercise testing

CPET is a commonly used and reliable noninvasive method to measure the cardiac and respiratory responses during a continuous graded exercise test from rest to maximum effort. CPET is normally conducted in a clinical setting in hospitals and health institutions. Several physiological variables are measured before, during, and after exercise. These include pulmonary function, minute ventilation ($\dot{V}E$), gas exchange, $\dot{V}O_{2\text{max}}$ or $\dot{V}O_{2\text{peak}}$, oxygen saturation, ECG features, and blood pressure (BP) (Figure 1). CPET also involves determination of the cardiopulmonary reserve and ventilatory limitation, and is used in the assessment of the risk of postoperative dyspnea. CPET is also a good method for detecting asymptomatic heart failure and coronary artery disease.\textsuperscript{10,11} Thus, CPET is indeed useful in the clinical setting for studying a patient’s exercise limitations and their causes.\textsuperscript{12}

![Cardiopulmonary exercise test by up-hill walking on the treadmill. Private photo with permission.](image)
2.2 Maximal oxygen uptake

\( \dot{V}O_2 \) max or \( \dot{V}O_2 \) peak* is considered the most important of the measurements taken during CPET.\(^1\) \( \dot{V}O_2 \) max was first described by Hill and Lupton in the 1920s\(^2\) and is defined as “the highest rate at which oxygen can be taken up and utilized by the body during severe exercise.”\(^3\) In accordance with the Fick principle,\(^4,5\) \( \dot{V}O_2 \) max is the product of maximal cardiac output (\( Q_{max} \)) and arteriovenous oxygen difference (\( (C_a-C_v)O_2 \) difference). Both maximal heart rate (HR\(_{max}\)) and arterial oxygen content are unrelated to aerobic exercise capacity;\(^6\) thus, variation between individuals in oxygen delivery to the working muscles reflects differences in stroke volume.

**Fick equation:**\(^4,5\)

\[
\dot{V}O_2 \text{max} = Q_{max} \cdot (C_a-C_v)O_2 \text{ difference}, \text{ where } Q_{max} \text{ is a function of HR}_{max} \text{ and stroke volume}
\]

Although \( \dot{V}O_2 \) max is measured in liters of oxygen per minute (L min\(^{-1}\)), it is usually expressed in milliliters of oxygen per kilogram of body weight per minute (mL kg\(^{-1}\) min\(^{-1}\)). \( \dot{V}O_2 \) max quantifies an individual’s aerobic exercise capacity and provides valuable diagnostic and prognostic information about the cardiorespiratory system. It is also a useful predictor of postoperative complications after pulmonary resection surgery\(^7\) and for assessing the timing of cardiac transplantation surgery.\(^8\)

\( \dot{V}O_2 \) max is task specific and is best measured during dynamic work that uses large muscle groups, such as walking or running.\(^9\) Consequently, \( \dot{V}O_2 \) max is 10–20% higher during uphill walking and running compared with cycling in both healthy individuals\(^10,11\) and in patients with lung disease.\(^12\) This is because recruitment of the quadriceps muscle is increased during uphill walking,\(^13,14\) and therefore, cardiac output may not be at its maximum. In addition, untrained subjects will usually terminate cycling exercise because of quadriceps fatigue.\(^15\) \( \dot{V}O_2 \) max is related to factors such as fitness level, genetics, age, sex, body size, hemoglobin concentration [Hb], and muscle mass,\(^16\) and is affected by the presence of diseases or medications that influence these components.\(^17\)

Endurance-trained individuals have a superior capacity to both deliver and utilize oxygen compared with untrained individuals, and cardiac output can be nearly twice as high in an elite athlete compared with an untrained person.\(^18\)

*In the present thesis, \( \dot{V}O_{2\text{peak}} \) is used when pre-defined criteria for maximum effort is not fulfilled.
Figure 2 shows four different physiological factors that can limit an individual’s $\dot{V}O_{2\text{max}}$. The first three factors (pulmonary diffusing capacity, cardiac output, oxygen-delivery capacity) are usually classified as “central factors” and the fourth (skeletal muscles) as “peripheral factor”. In normal individuals, 75–85 \% of $\dot{V}O_{2\text{max}}$ is limited by central factors during whole-body work and about 20 \% by peripheral factors. $\dot{V}O_{2\text{max}}$ in a young male elite endurance athlete may exceed 90 mL·kg\(^{-1}\)·min\(^{-1}\). $\dot{V}O_{2\text{max}}$ at any age is 10–20 \% lower in females than in males, in part because of a lower [Hb], more body fat, and a smaller heart in females. Longitudinal studies of healthy people have shown that the training-induced increase in $\dot{V}O_{2\text{max}}$ is primarily caused by an increase in $Q_{\text{max}}$ and not by an increase in systemic ($C_a$–$C_v$) $O_2$ difference. However, peripheral factors may be more important during exercise involving smaller muscle groups. Correspondingly, cardiac output decreases after prolonged bed rest and long-term use of beta-blockers.
It is reasonable to assume that lung cancer surgery affects all of the physiological factors mentioned above. Such effects can be direct because of removal of lung tissue and blood loss, and thus reduced diffusion and oxygen-carrying capacity, or indirect because of inactivity imposed by prolonged bed rest and severe pain, which leads to reduced cardiac output and loss of muscle mass. The extent of and exact mechanisms underlying these changes are not known. Decrement in the four factors mentioned above are accelerated by the use of chemotherapy and/or radiation, which affects all pathways of oxygen transport from the lungs to the working muscle. The oxygen-delivery capacity (DO₂) may thus be affected. DO₂ may be expressed as follows:

\[
DO_2 = cardiac\ output \cdot (Hb \cdot 1.39 \cdot SaO_2) + (PaO_2 \cdot 0.003)
\]

Cardiac output (predominantly stroke volume) is the main factor in the equation that can be manipulated by exercise training to keep the \( \frac{DO_2}{\dot{V}O_2} \) ratio constant in the working muscles. Exercise training may also lead to an increase in total blood Hb content because of an increase in blood volume.

### 2.2.1 Maximal oxygen uptake, mortality and survival

\( \dot{V}O_{2\text{max}} \) is a strong predictor of postoperative morbidity and mortality. This is also the case in patients with cardiopulmonary diseases such as cardiovascular disease and in lung cancer patients. In general, the change in physical fitness correlates strongly with the risk of mortality. Unfit individuals who improve their fitness status have shown a 35 % lower mortality risk compared with those who remain unfit. Thus, survival improves significantly when an unfit person becomes fit, and even small improvements in fitness level are associated with a significantly lowered risk of premature death. Correspondingly, \( \dot{V}O_{2\text{max}} \) is a good predictor of long-term survival. For example, an increase of only 3.5 mL\( \cdot \)kg\(^{-1}\)\( \cdot \)min\(^{-1}\) (corresponding to 1 MET*) is associated with 12 % and 17 % improvements in survival for men and women, respectively. Muscular strength, another important aspect of physical fitness, has shown to be independently and inversely associated with mortality in COPD patients, in cancer patients, and from all causes, even after adjusting for cardiorespiratory fitness. Strength training may also increase \( \dot{V}O_{2\text{max}} \), especially in severely deconditioned adults.

* Metabolic equivalent, equal to 3.5 mL oxygen per body weight per minute
2.2.2 Mechanisms of training effects on maximal oxygen uptake

In the scientific literature, an increase in $\dot{V}O_{2\text{max}}$ is the gold standard to demonstrate an aerobic training effect, and is a precise measurement to use when developing an exercise prescription or intervention. The magnitude of the increase after an intervention depends on a number of factors such as the training intensity, duration, and frequency, duration of the program, and the initial fitness status. The increase in stroke volume following exercise training leads to a reduced heart rate (HR) during submaximal exercise, which is caused by increases in left ventricular size, myocardial contractility, end-diastolic volume, and blood and plasma volumes. The oxygen-carrying capacity increases because of an increase in total blood Hb content, and the skeletal muscles may also require less blood flow because of an increase in the $(C_v-C_a)O_2$ difference. In addition, the capillarity of skeletal muscle increases, which improves the maximum muscle blood flow capacity and surface area available for gas exchange. Exercise training also delays blood lactate production and accumulation during exercise in both healthy individuals and patients with lung disease. Thus, fit muscles may require lower pulmonary ventilation than unfit muscles.

Table 1 presents a summary of the systematic reviews and meta-analyses of the changes in $\dot{V}O_{2\text{max}}$ after an exercise intervention in people with various conditions.

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>RCT included (n)</th>
<th>Participants (n)</th>
<th>Mean baseline $\dot{V}O_{2\text{max}}$ (mL·kg$^{-1}$·min$^{-1}$)</th>
<th>Increase in $\dot{V}O_{2\text{max}}$ (mL·kg$^{-1}$·min$^{-1}$ and %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang et al. (2005)$^{57}$</td>
<td>Healthy elderly</td>
<td>41</td>
<td>2102</td>
<td>23.2</td>
<td>3.4</td>
</tr>
<tr>
<td>Beauchamp et al. (2010)$^{56}$</td>
<td>Lung disease</td>
<td>8</td>
<td>388</td>
<td>Not reported</td>
<td>-0.01</td>
</tr>
<tr>
<td>Jones et al. (2011)$^{58}$</td>
<td>Adult cancer patients</td>
<td>6</td>
<td>571</td>
<td>Not reported</td>
<td>2.9</td>
</tr>
<tr>
<td>Valkeinen et al. (2010)$^{60}$</td>
<td>Coronary heart disease</td>
<td>21</td>
<td>922</td>
<td>Not reported</td>
<td>2.3</td>
</tr>
<tr>
<td>Weston et al. (2013)$^{59}$</td>
<td>Lifestyle induced cardio-metabolic disease</td>
<td>10</td>
<td>273</td>
<td>HIIT:22.5 MICE: 22.6</td>
<td>HIIT:5.4 MICE:2.6</td>
</tr>
<tr>
<td>Boule et al. (2003)$^{61}$</td>
<td>Type 2 diabetes mellitus</td>
<td>7</td>
<td>266</td>
<td>22.4</td>
<td>NR</td>
</tr>
</tbody>
</table>

HIIT= High-Intensity Interval Training, MICE= Moderate Intensity Continuous Training, n=number, RCT=randomised controlled trial
2.3 Other variables measured during CPET

In addition to $\dot{V}O_{2\text{max}}$, other variables can be measured directly before, during, and after CPET. The primary variables $\dot{V}O_2$, $\dot{V}CO_2$, tidal volume (Vt), respiratory rate (RR), and HR are used to derive secondary variables such as the respiratory exchange ratio (RER) ($\dot{V}CO_2/\dot{V}O_2$), $\dot{V}E$ (Vt × RR), oxygen pulse ($O_2$ pulse; $\dot{V}O_2$/HR), breathing reserve (maximal voluntary ventilation (MVV) – $\dot{V}E$/MVV), and the equivalents of $\dot{V}O_2$ and $\dot{V}CO_2$ ($\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$). Figure 3 shows an overview of the analyzers used during CPET and the primary and derived variables. This thesis focuses mainly on the variables measured during maximal exercise.

Figure 3. Overview of analyzers and variables during a CPET. Adapted from Cooper & Storer. ²
2.3.1 Ventilatory limitations and breathing reserve

The pulmonary transport of oxygen includes ventilation, diffusion into blood, and the chemical reaction with Hb. Jones and coworkers showed many years ago that there is a poor relationship between exercise capacity and FEV$_1$. This is because oxygen uptake from the lung to the working muscles is affected by many other factors such as cardiac output, arterial pO$_2$, Hb concentration, and leg blood flow. However, lung diseases can affect the ventilatory responses during exercise. Alterations in lung mechanics occurring in both obstructive and restrictive lung diseases lead to a reduction in ventilatory capacity, as measured by MVV. If severe enough, these reductions lead to early exercise limitations. Ventilatory limitation is normally defined as a breathing reserve < 15 %, calculated as (MVV – $\dot{V}_E$peak/MVV)$\times 100$, where $\dot{V}_E$peak denotes the maximum $\dot{V}_E$ achieved during CPET.

2.3.2 Ventilatory efficacy

Cardiopulmonary disease may also be associated with increased physiological dead space in the lungs, which must be compensated for by an increase in $\dot{V}_E$. This situation is reflected by an increased ventilation-to-work ratio and thus a steeper $\dot{V}_E$/CO$_2$ slope during exercise. Ventilatory inefficiency is measured as the linear relationship between $\dot{V}_E$ and CO$_2$ production ($\dot{V}_E$/CO$_2$ slope) and is considered a strong and independent prognostic predictor of survival in patients with heart failure, and in other patients with mild to moderate exercise limitation. A slope steeper than $\geq 34$ indicates an abnormal response. A steep $\dot{V}_E$/CO$_2$ slope is a marker of pulmonary hypertension in COPD patients, for whom a higher value is associated with reduced survival. In lung cancer patients, Torchio and coworkers have shown that a steep $\dot{V}_E$/CO$_2$ slope before surgery may be an independent predictor of mortality, even in the presence of acceptable physical function. This finding has not been confirmed by others.

2.3.3 Oxygen pulse

The exercise O$_2$ pulse is the volume of oxygen taken up by the pulmonary blood per heartbeat and provides valuable information during CPET. O$_2$ pulse is derived from a rearrangement of the Fick equation as follows:
\[ \dot{V}O_{2\text{max}} = SV \cdot HR \cdot (C_a - C_v) \text{ O}_2 \text{ difference} \]
\[ \dot{V}O_{2\text{max}} / HR = SV \cdot (C_a - C_v) \text{ O}_2 \text{ difference} \rightarrow \dot{V}O_{2\text{max}} / HR = \text{ O}_2 \text{ pulse} \]
\[ \text{O}_2 \text{ pulse} = SV \cdot (C_a - C_v) \text{ O}_2 \text{ difference} \]

The increase in \( \text{O}_2 \) pulse during CPET is usually smaller in patients with the most impaired ventricular responses during work,\(^6\) and appears as a low \( \text{O}_2 \) pulse in combination with normal oxygen saturation (\( \text{SpO}_2 \)) and Hb concentration. Hence, if \( \text{SpO}_2 \) and the Hb concentration are normal, the \( \text{O}_2 \) pulse may be a marker of stroke volume. The \( (C_a - C_v) \text{ O}_2 \) difference changes almost linearly from rest to maximal exercise both in fit normal subjects\(^6\)\(^9\) and in patients with heart failure.\(^7\) During hypoxemia (e.g., in a patient with lung disease), the \( (C_a - C_v) \text{ O}_2 \) decreases by 1 % for each 1 % decrease in \( \text{SpO}_2 \) below 96 %.\(^2\) Hence, patients with reduced oxygen delivery because of reduced oxygen content (e.g., hypoxemia, anemia, carboxyhemoglobin) may also have a low \( \text{O}_2 \) pulse.

\section*{2.3 Maximum effort during CPET}

During CPET, the subject’s motivation and effort, the equipment and the technician’s skills are important for ensuring valid and reliable results when for instance we want to compare groups in large epidemiological studies, and for the accurate interpretation of a maximal test in patients. An ability to achieve a maximum effort during CPET is also important in the pre-evaluation for lung cancer surgery because the patients’ \( \dot{V}O_{2\text{max}} \) may influence the choice of treatment (surgery vs. palliative care).\(^1\)\(^7\)\(^1\)\(^1\) Epidemiological studies and randomised controlled trials (RCTs) have shown that the end criteria for a maximum effort vary in current practice, which can be confusing. For example, the review by Howley and coworkers from 1995 found that 17 different criteria were used in 29 published articles.\(^7\)\(^2\) Unfortunately, little has changed since then, and knowledge about how these different end criteria are affected by sex and age is scarce. In addition, ACSM’s Guidelines for Exercise Testing and Prescription states that using a plateau in oxygen uptake has fallen into disfavor because a plateau is inconsistently seen during continuous graded exercise tests and is confounded by variations in the definitions and sampling.\(^7\)\(^3\) Thus, there is a need to develop consensus on the choice of criteria for determining whether a subject or patient has achieved \( \dot{V}O_{2\text{max}} \).
2.4 Non-Small-Cell lung cancer

Lung cancer has been the most common cancer in the world for several decades. Globally, 1.61 million people are diagnosed each year, and the incidence is increasing, especially among women and in developing regions such as Asia and Africa.\textsuperscript{74} There are differences between populations.\textsuperscript{75} In Norway, the total incidence was 2856 in 2013; the rate is decreasing in men, but is increasing among females.\textsuperscript{76}

Lung cancer is also the most common cause of cancer death and accounted for > 1.38 million deaths (18.2 % of the total) in 2008.\textsuperscript{74} In Norway, 2162 patients died of lung cancer in 2013.\textsuperscript{76} Thus, lung cancer still has a very high fatality rate, and the ratio of mortality to incidence is 0.76. Despite improved treatment strategies in recent years, the 5-year survival rate is < 15%.\textsuperscript{76}

2.4.1 Treatment

Surgical resection is the preferred treatment given with a curative intent whenever possible and offers the best prospect of long-term survival.\textsuperscript{77} After surgery, the 5-year relative survival rate is up to about 50 % for the most favorable tumor stages.\textsuperscript{78} However, at the time of diagnosis, only 23 % of all NSCLC patients were offered surgery in Norway between 2000 to 2007.\textsuperscript{78} For those who do not fulfill the criteria for surgery, the treatment options are chemotherapy and/or radiation therapy, and in a subgroup of patients also immunotherapy.\textsuperscript{79} The prognosis for survival for those who do not receive surgery is less than 8–10 %.\textsuperscript{78} Thus, surgery improves survival considerably.

2.4.1.1 Surgery

In Norway, surgical treatment of lung cancer is performed by board-certified thoracic surgeons at the university hospitals and involves the surgical excision of cancerous tissue from the lung with the intention of curing the patient. The surgery is accomplished through a muscle-sparing, nerve-sparing lateral thoracotomy or through video-assisted thoracoscopic surgery (VATS) without any rib spreading. The main surgical procedures are:

1) Pneumonectomy: removal of an entire lung
2) Lobectomy: removal of an entire lobe
3) Bi-lobectomy: removal of two entire lobes
4) Wedge resection: removal of part of a lobe
The duration of the hospital stay after surgery varies but is shorter for lobectomy or VATS compared with pneumonectomy. Fortunately, there have been improvements in the NSCLC resection rate (16% between 1996 to 2000 and 23% between 2001 to 2007), and postoperative mortality (4.8% in men and 1.7% in women). However, the waiting time from final diagnostic procedure until surgery has increased from 29 to 40 days over the past 20 years.

2.5 Preoperative evaluation for surgery

The European guidelines for preoperative functional evaluation in candidates for radical lung resection are produced by two different task forces. The European Respiratory Society/European Society for Thoracic Surgery (ERS/ESTS) guidelines are aimed at stratifying peri-operative risk of death and major cardiopulmonary complications, and at accepting or excluding patients from surgery. The British Thoracic Society/Society for Cardiothoracic Surgery (BTS/SCTS) guidelines focus more on discussing the risks of postoperative functional dyspnea and impaired quality of life with the patient and then letting the patient decide if he/she accepts the risk of surgery and its potential impacts on lifestyle. For predicting the risk of peri-operative or in-hospital deaths, the BTS/SCTS guidelines recommend use of the Thoracoscore instead of FEV₁, whereas the ERS/ESTS task force suggests a more frequent measure of \( \dot{V}O_{2\text{max}} \). The latter is preferred because \( \dot{V}O_{2\text{max}} \) has been reported as being a better predictor of postoperative morbidity and mortality than are FEV₁ and carbon monoxide lung diffusion capacity (DLCO). Hence, \( \dot{V}O_{2\text{max}} \) is now a pivotal measure in the ERS/ESTS algorithm in those patients with an FEV₁ or DLCO < 80% of predicted (Figure 4, page 12).

The use of CPET to evaluate the risk of NSCLC surgery has been examined extensively. However, the recent guidelines for the cutoff values are based mainly on data collected more than 15 years ago, which may not be accurate because of improvement in surgical techniques and in peri-and postoperative care. Most investigations still focus on male patients, with women comprising only 12% of the populations in the most recently published studies. In addition, the ERS/ESTS and BTS/SCTS guidelines use absolute cutoff values for \( \dot{V}O_{2\text{max}} \) in the algorithm regardless of sex and age.
The requirement for acceptance for surgery is thus higher in women despite their lower incidence of morbidity and mortality. This may exclude women from life-saving surgery which is an important aspect given the increasing prevalence of lung cancer in the female population.
2.6 Effects of surgery on physical function

The majority of investigations studying the change in $\dot{V}O_{2\text{max}}$ from before to after surgery have reported a decrease in $\dot{V}O_{2\text{max}}$ of both clinical and statistical significance, most pronounced after pneumonectomy (Table 2, page 14). However, the timing of the measurement of $\dot{V}O_{2\text{max}}$ ranges from 3 to 12 months after surgery. If the objective is to stratify the patient’s risk of early postoperative morbidity, there is a need for more knowledge about the change in $\dot{V}O_{2\text{max}}$ measured earlier after surgery. An evaluation time closer to the time when most complications occur may provide more accurate information for characterizing these patients in the more critical phase shortly after discharge from hospital.
### Table 2: Studies reporting change in maximal oxygen uptake ($\dot{V}O_{2max}$) after lung cancer surgery.

<table>
<thead>
<tr>
<th>Authors</th>
<th>FEV1 (% pred)</th>
<th>Number of subjects</th>
<th>Exercise mode</th>
<th>Measuring time after surgery (months)</th>
<th>% change in VO2max</th>
<th>Change in VO2max after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marcos et al. 1989</td>
<td>~ 81%</td>
<td>14</td>
<td>Bicycling</td>
<td>3 months</td>
<td>-13%</td>
<td>L: -13% P: -27%</td>
</tr>
<tr>
<td>Bolliger et al. 1995</td>
<td>67%</td>
<td>5</td>
<td>Bicycling</td>
<td>3 months</td>
<td>-4%</td>
<td>L: -4% P: -28%</td>
</tr>
<tr>
<td>Bollinger et al. 1996</td>
<td>~ 85%</td>
<td>50</td>
<td>Bicycling</td>
<td>3 months</td>
<td>-9%</td>
<td>L:  +1% P: -25%</td>
</tr>
<tr>
<td>Larsen et al. 1997</td>
<td>76%</td>
<td>16</td>
<td>Bicycling</td>
<td>6 months</td>
<td>13%</td>
<td>L: -13% P: -16%</td>
</tr>
<tr>
<td>Nezu et al. 1998</td>
<td>~ 85%</td>
<td>62</td>
<td>Bicycling</td>
<td>3 months</td>
<td>NR</td>
<td>L: NR P: NR</td>
</tr>
<tr>
<td>Bobbio et al. 2005</td>
<td>53%</td>
<td>11</td>
<td>Bicycling</td>
<td>3 months</td>
<td>-21%</td>
<td></td>
</tr>
<tr>
<td>Wang et al. 2006</td>
<td>86%</td>
<td>4</td>
<td>Bicycling</td>
<td>12 months</td>
<td>-12%</td>
<td>All: -12%</td>
</tr>
<tr>
<td>Kushibe et al. 2008</td>
<td>107%</td>
<td>95</td>
<td>Bicycling</td>
<td>6 months</td>
<td>-9.4%</td>
<td></td>
</tr>
<tr>
<td>Brunelli et al. 2012</td>
<td>86%</td>
<td>101</td>
<td>Bicycling</td>
<td>3 months</td>
<td>-5%</td>
<td></td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease, FEV1 = forced expiratory volume after one second, n = number, NR = not reported.
2.6.1 Predicting postoperative function

Knowledge about lung cancer surgery focuses mainly on morbidity and mortality risks, and the factors that affect functional outcomes, such as pulmonary function and $\dot{V}O_2\text{max}$ after surgery are poorly characterized. This is unfortunate because the health status after surgery can become significantly impaired\(^2\) and may include poor physical function and dyspnea from which patients fail to recover.\(^3\)

Some patients would not forgo surgery because the other options are encumbered with poorer prognosis, and it is important to be able to predict the functional outcomes as accurately as possible and to identify the associations between impairments in pulmonary function and cardiorespiratory fitness.

Lung function, in particular FEV\(_1\), DL\(_{CO}\), and predicted postoperative (ppo) FEV\(_1\) and DL\(_{CO}\), have traditionally been the key measures in the functional pre-evaluation for lung cancer surgery. These variables are thus included in the algorithms in both the European and American guidelines, by using the segment method.\(^1,7,11\)

The segment method is based on the principle that the amount of functional loss of lung segments is equivalent to the loss of FEV\(_1\) and DL\(_{CO}\);

$$\text{ppo} = \text{preoperative value} \times \frac{(19 - n \text{ segments resected})}{19 - \text{non functional segments}}$$

However, the use of lung function measurement has been questioned, especially in patients with severe COPD who show improvements in respiratory mechanics and elastic recoil because of the “lobar volume reduction effect.”\(^7\) In addition, the ppo segment method for predicting postoperative pulmonary function has been shown to produce conflicting results in terms of accuracy\(^9\) and the validation of this method has been performed months after surgery, when the most important complications have resolved.\(^7,9,15\)

For assessment of postoperative cardiorespiratory fitness, the ERS/ESTS guidelines also include the ppo $\dot{V}O_2\text{peak}$ in the algorithm and state that a ppo $\dot{V}O_2\text{max} < 10 \text{ mL kg}^{-1} \text{ min}^{-1}$ or 35% of predicted is a contraindication for major pulmonary resection (Figure 4, page 12).\(^1\) Consequently, this cutoff requires an accurate estimation to avoid excluding patients from life-saving surgery based on inaccurate data. However, from a physiological point of view, the relationship between ppo $\dot{V}O_2\text{peak}$ and actually measured postoperative $\dot{V}O_2\text{peak}$ does not seem reasonable because $\dot{V}O_2\text{peak}$ is determined by both central (pulmonary diffusing capacity, cardiac output, oxygen-carrying capacity) and peripheral factors.
(skeletal muscle factors), as discussed in detail on page 14. This cutoff also requires that the exercise test is performed to maximum in CPET involving the dynamic use of large muscle groups (e.g. treadmill). In many cases, it appears that the $\dot{V}O_2\text{peak}$ reported is submaximal because of the low peak HR relative to the predicted HR$_{\text{max}}$. Further studies are needed to validate the use of the ppo calculated by the segment method after surgery.

2.7 Training interventions in NSCLC patients

Exercise rehabilitation seems to be important for patients after resection of lung cancer because of their physical impairments prior to surgery, further loss in fitness after treatment, and knowledge that the physical fitness is associated with the prognosis after resection. However, to our knowledge, before the start of data collection for this thesis, only three studies have investigated the effect of exercise training in NSCLC patients undergoing surgery (Table 3). None of these studies used a randomised design, and only one study measured cardiorespiratory fitness by a directly measure of $\dot{V}O_2\text{peak}$. In addition, the number of participants included was low, the exercise duration was short, and the exercise intensity was low or moderate in all studies. Furthermore, the endurance exercise training comprised mainly continuous training of 20–45 min cycling, which is inappropriate in this population because of their poor leg strength and dyspnea, which is even more pronounced after surgery. Exercising for shorter periods at a higher intensity reduces the ventilatory response and allows the patient to recover between intervals, which may be more suitable for patients after lung resection. Muscular strength is generally poor, especially in COPD patients, and this can make cycling difficult for patients because of leg discomfort. However, no study has included resistance training in the exercise program. Importantly, even though the training effect was conflicting in these three studies, no adverse events were reported, and the feasibility of and adherence to the training program were adequate.

During and after the data collection in the present study, four RCT studies were published (Table 3, page 17). The results of these studies are discussed further in the Discussion section.
Table 3. Investigations studying the effect of exercise rehabilitation after NSCLC surgery before and after start of the present study (above and below the blue line, respectively).

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Number of subjects (M/F)</th>
<th>Localization (Country)</th>
<th>FEV\textsubscript{1}</th>
<th>DL\textsubscript{CO}</th>
<th>Study design</th>
<th>Type of exercise</th>
<th>Intensity</th>
<th>Frequency and length of intervention</th>
<th>(Primary) outcomes</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spuit et al. 2006</td>
<td>8/2</td>
<td>Netherlands</td>
<td>55 %</td>
<td>45 %</td>
<td>Non randomised pilot</td>
<td>Endurance</td>
<td>Strength</td>
<td>20 min non-stop at 60 % 3x15 repetitions at 60 % of 1RM</td>
<td>5 d/week for 8 weeks</td>
<td>6 MWD (m) Peak cycling load (watt)</td>
</tr>
<tr>
<td>Cesario et al. 2007</td>
<td>25 *</td>
<td>Italy</td>
<td>1.6</td>
<td>NR</td>
<td>Non randomised controlled trial</td>
<td>Cycling</td>
<td></td>
<td>30 min non-stop at 70-80 % of peak work load</td>
<td>5 d/week for 4 weeks</td>
<td>Pulmonary function 6 MWD (m)</td>
</tr>
<tr>
<td>Jones et al. 2008</td>
<td>10/9</td>
<td>USA</td>
<td>71 %</td>
<td>83 %</td>
<td>Non randomised pilot</td>
<td>Cycling</td>
<td></td>
<td>20 - 45 min non-stop at 60-70 % of peak work load. Interval training in four sessions</td>
<td>3 d/week for 14 weeks</td>
<td>( \dot{V}O_2 \text{peak} )</td>
</tr>
<tr>
<td>Arbane et al. 2011</td>
<td>51</td>
<td>United kingdom</td>
<td>1.9 L</td>
<td>NR</td>
<td>Randomised controlled trial</td>
<td>Walking</td>
<td>Adapted home strengthening program</td>
<td>In-patient sessions Home based program: walking in the park Strength training</td>
<td>5 days</td>
<td>6 MWD (m)</td>
</tr>
<tr>
<td>Peddle-McIntyre et al. 2012</td>
<td>7/10</td>
<td>Canada</td>
<td>77 %</td>
<td>NR</td>
<td>Non randomised controlled trial</td>
<td>Resistance training</td>
<td>Breathing</td>
<td>From 60 % to 85 % 1RM</td>
<td>3 d/week for 10 weeks</td>
<td>Muscular strength 6 MWD</td>
</tr>
<tr>
<td>Stigt et al. 2013</td>
<td>40/9</td>
<td>Netherlands</td>
<td>85 %</td>
<td>NR</td>
<td>Randomised controlled trial</td>
<td>Cycling</td>
<td>Muscle training</td>
<td>60 - 80 % of peak work load</td>
<td>2 d/week for 12 weeks</td>
<td>QOL Pulmonary function 6 MWD</td>
</tr>
<tr>
<td>Arbane et al. 2014</td>
<td>72/59</td>
<td>United kingdom</td>
<td>2.5 L</td>
<td>NR</td>
<td>Randomised controlled trial</td>
<td>Cycling</td>
<td>Home walking program</td>
<td>60 - 90 % of HRR Borg 13-15</td>
<td>Daily for 4 weeks</td>
<td>Physical activity QOL ISWT Quadriceps force</td>
</tr>
<tr>
<td>Salhi et al. 2014</td>
<td>24/49</td>
<td>Belgium</td>
<td>85 %</td>
<td>75 %</td>
<td>Randomised controlled trial</td>
<td>Resistance training</td>
<td></td>
<td></td>
<td></td>
<td>MCSA Quadriceps force</td>
</tr>
</tbody>
</table>

* active participants, ¶ only 15 of the included patients underwent surgery

BGD = between-group difference, DL\textsubscript{CO} = Diffusion Capacity for Carbon Monoxide in the Lung, FEV\textsubscript{1} = Forced Expiratory Volume after 1 sec, HRR = Heart Rate Reserve \((HR_{max} - HR_{rest}) \cdot \% \text{ intensity} + \text{ rest})\, ISWR = Incremental Shuttle Walk Test, MWD = Minute Walking Distance, MCSA = Muscle Cross Sectional Area, NR = Not Reported, RM = Repetition Maximum, \( \dot{V}O_2 \text{peak} \) = Peak Oxygen Uptake, QOL = Quality of Life
3.0 NEED OF NEW INFORMATION

As shown in Table 4, reference values during CPET have previously been reported, either for $V_{O2max}$ alone,104-106 or in combination with other cardiorespiratory variables typically used during a CPET.109-114 However, the majority of these studies are old,104,106,108-111,113 are based on small samples, are without randomly selected participants,108,109,110,115,116 and the number of elderly and female participants are low or absent.110-112,116 To interpret the results of a CPET, normative reference values are thus required, derived from the same subjects and using similar test-methods.

Table 4. Reference values in different populations published from 1960 and after start of the present study (above and below the blue line, respectively).

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Country</th>
<th>Gender</th>
<th>Number (n)</th>
<th>Age (year)</th>
<th>Ergometer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Åstrand, 1960</td>
<td>Healthy</td>
<td>Sweden, US</td>
<td>F/M</td>
<td>44</td>
<td>6-65</td>
<td>Cycle</td>
</tr>
<tr>
<td>Bruce et al., 1973</td>
<td>General population</td>
<td>US</td>
<td>F/M</td>
<td>157/138</td>
<td>29-73</td>
<td>Treadmill</td>
</tr>
<tr>
<td>Drinkwater et al., 1975</td>
<td>Healthy</td>
<td>US</td>
<td>F</td>
<td>109</td>
<td>6-68</td>
<td>Treadmill</td>
</tr>
<tr>
<td>Jones et al., 1985</td>
<td>Students</td>
<td>Canada</td>
<td>F/M</td>
<td>100</td>
<td>15-71</td>
<td>Cycle</td>
</tr>
<tr>
<td>Hansen et al., 1984</td>
<td>Shipyard workers</td>
<td>US</td>
<td>M</td>
<td>265</td>
<td>34-74</td>
<td>Cycle</td>
</tr>
<tr>
<td>Vogel et al., 1986</td>
<td>US Army</td>
<td>US</td>
<td>F/M</td>
<td>1889</td>
<td>17-55</td>
<td>Treadmill</td>
</tr>
<tr>
<td>Inbar et al., 1994</td>
<td>Healthy workers</td>
<td>Israel</td>
<td>M</td>
<td>1424</td>
<td>20-70</td>
<td>Treadmill</td>
</tr>
<tr>
<td>Fairbarn et al., 1994</td>
<td>Healthy</td>
<td>Canada</td>
<td>F/M</td>
<td>231</td>
<td>20-80</td>
<td>Cycle</td>
</tr>
<tr>
<td>Paterson et al., 1999</td>
<td>Healthy</td>
<td>Canada</td>
<td>F/M</td>
<td>298</td>
<td>55-86</td>
<td>Treadmill</td>
</tr>
<tr>
<td>Neder et al., 1999</td>
<td>Sedentary</td>
<td>Brazil</td>
<td>F/M</td>
<td>120</td>
<td>20-80</td>
<td>Cycle</td>
</tr>
<tr>
<td>Davis et al., 2002</td>
<td>Sedentary</td>
<td>US</td>
<td>F/M</td>
<td>230</td>
<td>20-70</td>
<td>Cycle</td>
</tr>
<tr>
<td>Nelson et al., 2010</td>
<td>Healthy</td>
<td>Canada</td>
<td>M</td>
<td>816</td>
<td>30-69</td>
<td>Treadmill</td>
</tr>
<tr>
<td>Aspenes et al., 2011</td>
<td>Healthy</td>
<td>Norway</td>
<td>F/M</td>
<td>4631</td>
<td>20-90</td>
<td>Treadmill</td>
</tr>
<tr>
<td>Loe et al., 2013</td>
<td>Healthy</td>
<td>Norway</td>
<td>F/M</td>
<td>3816</td>
<td>20-90</td>
<td>Treadmill</td>
</tr>
</tbody>
</table>

F = female, M= male, n = number, US=United State of America
A valid $\dot{V}O_2\text{max}$ and defining cardiopulmonary reserve during CPET are important and depend entirely on the individuals’ ability to cope with exhaustion, especially when the result determines whether a patient gets access to potentially curative treatment strategies. The technicians’ skills and the subjects’ motivation and effort are important requirements to ensure valid and reliable results when comparing groups in large epidemiological surveys, as well as for the accurate interpretation of a maximal test for both athletes and patients. The classical plateau described by Taylor and coworkers is recognized as the gold standard to determine a true $\dot{V}O_2\text{max}$. However, this criterion is based on old measurement techniques, different protocols and are developed from athletes, children or adolescents, and is thus not straightforward to use in practical settings. During the preoperative evaluation for lung cancer, maximal effort is especially important to secure a valid $\dot{V}O_2\text{max}$. Poor effort gives lower values, and may in the worst case lead to misinterpretation during the preoperative evaluation. Thus, new recommendation for maximal effort during CPET is needed.

Not surprisingly, many lung cancer patients are deconditioned with poor cardiorespiratory fitness. After surgery, the health status becomes further impaired, with dyspnoea failing to recover. It is, however, important to know the effect of lung cancer surgery on CRF related to the extent of the operation, for preventing further impairment, and for predicting the functional outcomes as accurate as possible. Therefore, an evaluation of the changes in CRF from before to after surgery, and the ability to predict postoperative outcomes is needed. In addition, individual exercise training for reversing the negative effects of treatment may be especially important for these patients. However, knowledge about feasibility and effects after high-intensity endurance- and strength training are lacking.
3.1 Aims

Based on the above, the specific aims of the present thesis were as follows:

Part one – normative variables in healthy individuals

1. To determine the cardiorespiratory response during maximal exercise in a well-described representative national sample of 20- to 85-year-old men and women (paper I).

2. To describe the different end criteria used for defining $\dot{V}O_{2\text{max}}$ during a maximal progressive graded exercise test on the treadmill in a healthy sample of 20-to 85-year-old men and women, and to explore if the choice of end criteria has an impact on the $\dot{V}O_{2\text{max}}$ value (paper II).

Part two – lung cancer surgery, cardiorespiratory fitness and effects of exercise training

3. To evaluate the effect of lung cancer surgery on cardiorespiratory fitness measured on a treadmill, and to assess the agreement between predicted postoperative and actually measured postoperative $\dot{V}O_{2\text{peak}}$ values (paper III).

4. To evaluate the effects of high-intensity endurance- and strength training shortly after lung cancer surgery on $\dot{V}O_{2\text{peak}}$, pulmonary function, muscular strength, total muscle mass, daily physical functioning and QoL through a randomised controlled trial (paper IV).
4.0 PARTICIPANTS AND METHODS

4.1 Study design

The thesis is based on two separate studies – “Physical Activity among Adult and Older People Study” (KAN) (paper I and II), and “Fitness Activity and Lung Cancer Study” (FALC) (paper III and IV). Paper I and II are based on a multicenter cross-sectional study, while paper III had a longitudinal prospective study design, and paper IV had a single blinded randomised control design (Table 5). Totally 759 participants were included in paper I and 804 participants in paper II, 70 patients were included in paper III and 68 patients in paper IV.

Table 5. Design of the four included papers

<table>
<thead>
<tr>
<th>Paper</th>
<th>Number</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>759</td>
<td>Cross-sectional multicenter study</td>
</tr>
<tr>
<td>II</td>
<td>804</td>
<td>Cross-sectional multicenter study</td>
</tr>
<tr>
<td>III</td>
<td>70</td>
<td>Longitudinal prospective study</td>
</tr>
<tr>
<td>IV</td>
<td>68</td>
<td>Single blinded randomised controlled trial</td>
</tr>
</tbody>
</table>

Paper I and II

In paper I and II, we performed a cross-sectional multicenter study involving nine regional test laboratories throughout Norway (Figure 5, page 22). The laboratories were chosen based on population density involving universities or college universities that had a sport science curriculum. One laboratory had to be withdrawn before start due to lack of equipment (nr 8, Figure 5, page 22). The Norwegian School of Sport Sciences in Oslo coordinated the study.
PARTICIPANTS AND METHODS

This was a longitudinal prospective designed study investigating 70 patients who underwent lung cancer surgery at Oslo University hospital or Akershus University hospital from November 2010 to September 2012. Patient with suspected stage I to IIIA NSCLC, who were candidates for primary surgery with curative intent, were invited to participate. ERS/ESTS clinical guidelines were used as a criterion for operability.\(^1\)

**Paper IV**

Four to six weeks after surgery, 61 out of 68 patients were randomised into a single blind, controlled trial randomly allocated into two groups in a 1:1 ratio within four stratification groups; 1) no COPD - no treatment of postoperative chemotherapy; 2) no COPD – treatment of postoperative chemotherapy; 3)
having COPD – no treatment of postoperative chemotherapy; 4) having COPD – treatment of postoperative chemotherapy. The randomised treatment assignments were concealed in opaque envelopes by an external off-site statistician and were opened individually by the patient at the end of the visit.

4.2 Participants

Part I:
A total of 3485 individuals from all parts of Norway underwent objective measurements of physical activity in the KAN1 study in 2008-09.124 They were all previously drawn from a representative sample by the Norwegian population registry. From KAN1, a cohort of 1,930 men and women age 20-85 years were randomly selected to participate to perform a CPET. A total of 904 participants met at the laboratory. In paper I, 759 healthy participants*, of the total 904 participants, fulfilled CPET based on defined end-criteria for RER and rating of perceived exertion. In paper II, 804 healthy participants, of the 904 participants, fulfilled CPET until voluntary exhaustion. The flow chart of the recruitment strategy and inclusion profile for Part I (paper I and II) are presented in Figure 6, (page 24) and the baseline characteristics of the participants are listed in Results.

Part II:
From November 2010 throughout September 2012, a total of 106 patients were screened to participate in the FALC study involving NSCLC patients. Of these patients, 77 voluntaire to participate in a follow up after surgery and/or in the exercise RCT (Figure 7, page 25). Unfortunately, 10 patients were not able to participate in the exercise trial because of a parallel ongoing study or lack of fitness centers in an acceptable distance from their homes, but these patients were included in paper III. The baseline characteristics of the NSCLC patients are listed in Results.

* Healthy condition was defined as absence of any medical treated disease that could affect the participants’ fitness status (e.g heart disease, COPD, stroke, disability).
4.3 Ethics

**Paper I and II:** The study was approved by the Regional Committee for Medical Ethics (REK South-Eastern Norway B, S-08046b) and the Norwegian Social Science Data Services AS. All individuals signed written informed consent forms before participating.
**PARTICIPANTS AND METHODS**

**Paper III and IV**: The FALC study was conducted in accordance with the CONSORT statement for non-pharmacologic interventions, and was approved by the Regional Committee for Medical Ethics before enrolment (REK Sør-Øst B, 2010/2008a). All participants provided written informed consents before surgery. No sponsor had any role in the study regarding design, data collection, analyses, interpretation of the data or preparation of the manuscript. The study is listed in the ClinicalTrials.gov Protocol Registration System (NCT01748981).

**Figure 7. Flowchart of the recruitment strategy and inclusion in part II of the thesis (FALC).**
4.4 Methods and test procedures

All participants were advised to take their regular medications prior to the investigation. In addition, all NSCLC patients received salbutamol and ipratropium bromide 30 min before the tests for optimizing the pulmonary function. Between the second and third measurement, 33% of the participants received four cycles of adjuvant chemotherapy. However, no NSCLC patients were receiving chemotherapy or radiation therapy during the test period.

4.4.1 Anthropometry and body composition

In all participants, height and body weight were measured to the nearest 0.5 cm and 0.1 kg, respectively, with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight/height$^2$ (kg/m$^2$).

In paper I, percent fat for estimation of FFM was determined using a three site skin fold measurements by a skin fold caliper. The measurements were recorded at the chest, abdomen and thigh for the men and at the triceps, suprailium and thigh for the women. The following equation was used for percent fat: \[ \text{Percent Fat} = \frac{495}{\text{Body Density}} - 450. \]

Gender-specific equations were used for estimating the body density.\(^{127,128}\)

In paper IV, total muscle mass of the whole body were measured with the use of dual-energy x-ray absorptiometry in the total body scanning mode (GE Lunar Prodigy, GE Healthcare, Madison, Wisconsin, USA) (Figure 8, page 27).

4.4.2 Pulmonary function

Pulmonary function measurements by maximum expiratory flow-volume loops were conducted according to the American Thoracic Society/European Respiratory Society guidelines.\(^{129}\) Forced Expiratory Volume (FEV$_1$) and forced vital capacity (FVC) were recorded. Reference values based on the equations from ERS 1993 update were used in all papers.\(^{130}\)

Ventilatory capacity was estimated by FEV$_1$ ∙ 35 and 40 in paper I,\(^{2,131}\) and directly measured by MVV in paper III and IV. The patient was asked to breathe as fast and deep as possible for 12 seconds in a standing position. The highest value was recorded as maximal ventilatory capacity. For those few patients who did not manage the test procedure, the FEV$_1$ ∙ 40 was used.\(^{131}\)

Diffusion capacity in the lungs for carbon monoxide (DL$_{CO}$) (paper III and IV) were measured in a sitting position inhaling carbon monoxide and methane according to guidelines.\(^{132}\)
4.3 Cardiopulmonary exercise test

For all participants, CPET was performed by walking and running on the treadmill (Woodway, Würzburg, Germany) until exhaustion using a modified Balke protocol. All the participants underwent a pre-test on the treadmill to ensure that they were familiar with treadmill walking before the test began. Three to four minutes of warm-up and steady state measurements were conducted with an inclination set at 4%. In the healthy population (Part I), the treadmill speed was set to 3.8 or 4.8 km·h⁻¹ based on age. In the...
NSCLC patients, the speed was set between 1.8 – 4.8 km·t⁻¹ based on age or the predicted fitness level. After warm-up, the inclination then increased each 60 sec by two percent up to 20% inclination for all participants. If the participant was still able to continue, the speed then rose by 0.5 km·t⁻¹ until exhaustion. The test was ended when the participant was unable to continue, despite encouragement from the technician.

Gas exchange and ventilatory variables were continuously measured by breathing into a Hans Rudolph two-way breathing mask (2700 series; Hans Rudolph Inc, Kansas City, USA). The mask was connected to the metabolic cart to assess the oxygen and carbon dioxide content of expired air for calculation of $\dot{V}O_2$.

HR was recorded each minute from a Polar sports watcher in paper I and II, and by a 12-lead ECG record in paper III and IV (Cardiosoft, GE Marquette Medical Systems, Milwaukee, USA).

The oxygen saturation was measured with a finger probe using a stationary pulse oximeter in paper III and IV (NONIN 8600, Medical, Inc., Minneapolis, USA).

The rating of perceived exertion was obtained using the Borg scale 6–20 frequently asked during the CPET and as soon as possible after termination.

A capillary blood lactate sample was taken about 60 sec after termination of the exercise test in all participants (KDK, Japan or ABL 700 series, Radiometer, Copenhagen, Denmark).

### 4.4.3.1 Data handling

Maximal minute ventilation ($\dot{V}_{E,max}$), $\dot{V}O_2$, carbon dioxide output ($\dot{V}CO_2$), and the respiratory exchange ratio (RER) were reported as 30-second averages. Only in paper I, the participant was excluded from the analyses if RER < 1.10 or the Borg 6–20 score was < 17.

The $O_2$ pulse was calculated by dividing $VO_{2max}$ (in milliliters) by the maximum heart rate ($HR_{max}$). The breathing reserve (%) was calculated using the following equation: \[ \left( \frac{MVV - \dot{V}_{E,max}}{MVV} \right) \times 100. \]

Levelling off in paper I and II were defined as a plateau in $\dot{V}O_2$ as any two 30-sec $\dot{V}O_2$ values in which the second was not higher than the first, provided increase in ventilation at maximal effort. Participants who did not exhibit an increase in ventilation despite achievement of a plateau were not accepted. This was in order to ensure that the leveling off was caused by reaching the respiratory compensation point due to metabolic acidosis, and not by variation in the $\dot{V}i$ during the test (Figure 9, page 29).
Information about co-morbidity in the FALC study (Part II) was collected from the patient records a few days before surgery and by a consultant. Major cardiopulmonary complications that occurred within 30 days after surgery were recorded, and included; atelectasis, arrhythmia, cardiac failure, myocardial infarct, pneumonia, pulmonary embolism, respiratory failure.\textsuperscript{135}

All CPET values obtained in paper III and IV were expressed as percentage of predicted values based on the equations derived from paper I.\textsuperscript{136}

In paper III, the extent of the surgery (i.e. wedge resection, lobectomy, bi-lobectomy or pneumonectomy) and number of functional segments actually removed were recorded after surgery,
and the postoperative $\dot{V}O_{2peak}$ was calculated using the remaining functional segment technique (page 15). The functional segment calculation was estimated by bronchoscopy, lung perfusion scan or computed tomography. For patients undergoing wedge resection, the value 1 was used per segment.

4.4.3.2 $\dot{V}O_{2peak}$ vs $\dot{V}O_{2max}$

None of the participants in paper III or IV were excluded based on specified end-criteria for reaching maximal effort during CPET. Thus, in the NSCLC patients, the reported $\dot{V}O_2$ value is more properly referred to as $\dot{V}O_{2peak}$ rather than $\dot{V}O_{2max}$, even though there was evidence of fulfilling the end criteria recommendations (paper II) in the majority of the patients (78% pre surgery).

4.4.4 Muscular strength and physical fitness (paper IV)

In paper IV, concentric leg strength was assessed by the sum of the maximum weight that could be lifted once (1RM) using a horizontal hip and knee extension movement with a starting angles of 90° flexion (leg-press). After a short warm up with light weights to ensure good quality, resistance was added until the participant was clearly unable to lift more, reported a symptom that required stopping, or until the participant refused to try to lift more.

Maximum hand strength was measured by a grip strength dynamometer (Baseline 90 kg/Chattanooga), and the best of three attempts was recorded.

Measures of daily physical functioning included, “Chair stand”, maximum stair run for 15 seconds and a modified “One foot balance test” for maximum 60 seconds while standing on a soft ground.

4.4.5 Physical activity (paper I)

The ActiGraf GT1M activity monitor (ActiGraf, LLC, Pensacola, FL, USA) was used in paper I for measurements of the participants physical activity level for seven consecutive days prior to CPET. This monitor is a small accelerometer that registers vertical acceleration in counts per minute (CPM), expressed as the total number of registered counts for all valid days, divided by wearing time. Only data were included if the participants had accumulated at least 10 hours of activity recordings per day for a minimum of four days. Both CPM and steps per day were reported.
4.4.6 quality of life (paper IV)

The Medical outcomes 36-item Short Form Health Survey (SF-36) was used to evaluate quality of life (QoL), focusing on the physical component summary score and the mental component summary score. Higher scores indicated better QoL, ranging from 0 - 100.

Score of dyspnoea was measured by European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QOL-C30), ranging from 0-100, where lower scores indicated lower dyspnoea.

4.4.7 Surgery procedure (paper III and IV)

Surgical treatment was performed by on board-certified thoracic surgeons through a muscle-sparing, nerve-sparing lateral thoracotomy or through a video assisted thoracoscopic surgery without any rib spreading. An epidural catheter for postoperative pain relief was offered to all patients. Chest tubes were routinely placed on water seal immediately postoperatively and removed when no air leak was present. No pre- or postoperative rehabilitation or training was provided, but all patients were regular seen by a physiotherapist for general mobilisation, cough assistance and mucus clearance until discharge.

4.4.8 Training intervention (paper IV)

The exercise program was given in groups and individually one by one at selected fitness centers nearby the patient’s home, three hours per week for 20 weeks, and started one week after randomisation. Highly qualified personal trainers and physiotherapists were responsible for conducting the exercise program. The exercise program was individualized and included a cardiovascular warm-up, interval training, progressive resistance training (PRT), and daily inspiratory muscle training. The intervention focused on high-intensity training, mainly by uphill walking on a treadmill at 80-95 % of the maximal heart rate and PRT in three series at 6-12 RM by leg press, back extension, seat row, chest press and front raises.

The first four weeks, the patients were introduced to the program while focusing on safety, techniques and familiarization. The endurance intensity and strength load were then continuously increased based on the patients’ improvement, cooping of dyspnea, and feelings of well-being or fatigue on each exercise day. Patients in the control group were not given any advice about exercise beyond general information from the hospital.
4.4.9 Quality control (paper I-IV)

In paper I and II, three types of metabolic carts were used in the nine test centers: Jaeger Oxycon Pro (Würzburg, Germany; n = 2), Vmax SensorMedics (Yorba Linda, California, USA; n = 6), and the Moxus Modular VO₂ system (Philadelphia, USA; n = 1). In paper III and IV, Vmax SensorMedics (Yorba Linda, California, USA) was used. To ensure valid measurements, all analyzers were volume- and gas-calibrated according to the manufacturers’ recommendations each morning and throughout the day. The calibration factor was always corrected for humidity and room temperature. The analyzers were also checked for measurement precision and accuracy at two different points with a standardized motorized mechanical lung (Motorized Syringe with Metabolic Calibration Kit, VacuMed, Ventura, USA) (Figure 10), and/or a human calibrator. Based on the results, a correction factor was calculated for each gas analyzer in paper I and II to ensure reliable and comparable data between the test laboratories. The average calculation factor was 0.990 SD ± 4.76 (range 0.925 to 1.059).

Figure 10. Checking the precision and accuracy of the metabolic equipment at the University of Agder, Kristiansand, using a motorized mechanical lung (VacuMed, Ventura, USA).
PARTICIPANTS AND METHODS

All lab technicians involved in the data gathering were experienced technicians and rigorously trained in the test procedures, both locally and at regular inter-laboratory meetings. In addition, the nine treadmills involved in this thesis were pre-programmed to ensure that identical exercise Balke protocols were used both in the healthy participants and in the NSCLC patients.

4.5. Statistics

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS software, version 21.0; IBM Corp., Armonk, NY, USA).

Demographic data are presented as mean ± standard deviation (SD) for continuous variables, median and range for nonnormally distributed variables, and proportions for binary variables. Cross-sectional data are reported by age and sex, and are grouped into 10-year cohorts in paper I and 15-year cohorts in paper II.

Analysis of variance (ANOVA) was used to evaluate differences in the cardiorespiratory variables between age groups.

Linear regression analysis was performed according to age for $\dot{V}O_{2\max}$ and HR$_{\max}$ in paper I.

Differences between the sexes were analyzed using Student’s t test in papers I and II, and differences between pre- and postsurgery variables were analyzed using Student’s paired t test in paper III.

Correlations were assessed using Pearson’s correlation coefficient (r) between the commonly accepted end criteria in paper II and between effect size and $\dot{V}O_{2\text{peak}}$ in paper IV.

Linear correlations ($r^2$) and the limits of agreement through a Bland–Altman plot are reported between the ppo and actually measured variables in paper III.

Simple linear regression was used to determine the relationships between the changes from before to after surgery in different CPET variables (independent variables) and change in $\dot{V}O_{2\text{peak}}$ (dependent variable).

Multiple linear regression was used to study the contribution to the adjusted squared multiple correlation coefficient by including different sets of independent variables.
Sample size calculations in paper IV were based on the primary outcome of a change in $\dot{V}O_{2\text{peak}}$ of 4.0 mL·kg$^{-1}$·min$^{-1}$, assuming an SD of 4.6 mL·kg$^{-1}$·min$^{-1}$ (estimated from the study by Kushibe and coworkers). A sample size of 21 per group for 80% power was required to detect the assumed difference between means with a 5% significance level.

Effects after exercise training were evaluated on an intention-to-treat basis. Missing values were imputed using a multiple-imputation model for all of the 61 randomised patients. Because dropping out was not expected to be related to the treatment allocation, we assumed that missing patient data at the end were grossly at random. Per-protocol analyses were also evaluated for the primary outcome where the analysis included a comparison between all exercising patients and the nonexercising patients. $p$ values were calculated using the chi-square test for categorical variables and analysis of covariance (ANCOVA) for continuous variables. A $p$-value $\leq 0.05$ was accepted as significant in all papers.
SUMMARY OF RESULTS

5.0 SUMMARY OF RESULTS

5.1 Paper I

Reference Values for Cardiorespiratory Response and Fitness on the Treadmill in a 20- to 85-Year-Old Population

In this cross-sectional study, the objective was to study the cardiorespiratory response during maximal exercise in a representative national sample of healthy and well described 20- to 85-year old men and women. A total of 394 men and 365 women successfully achieved the \( \dot{V}O_{2\text{max}} \) (84 %) based on the end criteria chosen for an acceptable \( \dot{V}O_{2\text{max}} \) (RER \( \geq 1.10 \) or a Borg score of \( \geq 17 \)). The baseline characteristics of all participants meeting at the laboratory are given in Table 6.

Table 6. Baseline characteristics of all the voluntary participants in part I of the thesis (n=904)

<table>
<thead>
<tr>
<th></th>
<th>Men (n=462)</th>
<th>Women (n=442)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>51.0 ± 14.5</td>
<td>51.6 ± 15.1</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>179.3 ± 6.6</td>
<td>166.1 ± 6.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84.5 ± 12.0</td>
<td>69.9 ± 12.7</td>
</tr>
<tr>
<td>BMI (kg·m(^{-2}))</td>
<td>26.3 ± 3.4</td>
<td>25.3 ± 4.3</td>
</tr>
<tr>
<td>Activity level, accelerometer (counts·min(^{-1}))</td>
<td>359 ± 138</td>
<td>355 ± 132</td>
</tr>
<tr>
<td>Activity level, accelerometer (steps·day(^{-1}))</td>
<td>8815 ± 11791</td>
<td>8643 ± 2783</td>
</tr>
<tr>
<td>Smokers, No. (%)</td>
<td>67 (15)</td>
<td>65 (15)</td>
</tr>
<tr>
<td>Education level, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>46 (10)</td>
<td>54 (12)</td>
</tr>
<tr>
<td>High school</td>
<td>174 (38)</td>
<td>141 (32)</td>
</tr>
<tr>
<td>University, &lt; 4 years</td>
<td>109 (24)</td>
<td>108 (25)</td>
</tr>
<tr>
<td>University, ≥ 4 years</td>
<td>124 (27)</td>
<td>134 (31)</td>
</tr>
</tbody>
</table>

BMI = Body mass index, n = number
SUMMARY OF RESULTS

1. In the 20- to 29-year-old age group, $\dot{V}O_{2\text{max}}$ (mL·kg$^{-1}$·min$^{-1}$) was 40.3 ± 7.1 in women and 48.6 ± 9.6 in men, and declined linearly by 8 % per decade after age 30 years in both sexes. The predictive equation was described by the following equation for men: $\dot{V}O_{2\text{max}} = 60.9 - 0.43 \times \text{age}$ ($r = 0.61, \text{CI: 0.54-0.67}$) and for the women: $\dot{V}O_{2\text{max}} = 48.2 - 0.32 \times \text{age}$ ($r = 0.61, \text{CI: 0.54-0.67}$).

2. Maximal HR was 194 beat·min$^{-1}$ ± 7.8 in the 20-29-year age cohort and declined with age by ± 7.6 per cohort. The predictive equation was described by the following equation for men: $HR_{\text{max}} = 220 - 0.88 \times \text{age}$ ($r = 0.7, \text{CI: 0.65-0.75}$), and for women: $HR_{\text{max}} = 208 - 0.66 \times \text{age}$ ($r = 0.7, \text{CI: 0.64-0.75}$).

3. The maximal $O_2$ pulse was 33 % lower in women ($P < 0.001$), and decreased significantly with age in both sexes by 5 % and 3 % per decade for women and men, respectively.

4. Women’s maximal minute ventilation was 66 % that of men ($P < 0.001$) and decreased with age after 40–49 years in both sexes. The breathing reserve was 30 % (± 13.7 %) in women and 23 % (± 12.8 %) in men ($P < 0.001$), with no age-related differences.
5.2 Paper II

*End Criteria for Reaching Maximal Oxygen Uptake Must Be Strict and Adjusted to Sex and Age: A Cross-Sectional Study*

The objective of paper II was to describe different end criteria for reaching $\dot{V}O_{2\text{max}}$ during a progressive maximal treadmill test in a healthy sample of 20-85-year-old men and women, and to explore if the choice of end criteria had an impact on the $\dot{V}O_{2\text{max}}$ variable. Four hundred and fifteen men and 389 women (93 %) fulfilled the exercise test until voluntary termination.

1. Forty-one percent of the women and 42 % of the men achieved a plateau in $VO_2$. There were no sex-related differences in $HR_{\text{max}}$, RER, or Borg Scale rating. The blood lactate concentration was 18 % lower in women ($P < 0.001$). Both RER and blood lactate was decreasing, especially after 50 years of age. The maximum end criteria variables are given by gender and 15-yrs age cohort in paper II, Table 2.

2. When using RER $\geq 1.15$ or blood lactate concentration $\geq 8.0 \text{ mmol} \cdot \text{L}^{-1}$, $\dot{V}O_{2\text{max}}$ was 4 % ($P = 0.012$) and 10 % greater ($P < 0.001$), respectively when compared to voluntary termination. A blood lactate concentration $\geq 8.0 \text{ mmol} \cdot \text{L}^{-1}$ excluded 63 % of the participants in the 50-85-year-old cohort.

3. Suggestions for new recommendations for reaching maximal oxygen uptake are given in Table 7, page 38.
Table 7. New recommendations for maximal effort for haemolysed post exercise blood lactate and respiratory exchange ratio (RER). Both criteria must be fulfilled.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Blood lactate concentration† (\text{mmol}\cdot\text{L}^{-1})</th>
<th>RER (\frac{\dot{V}CO_2}{\dot{V}O_2})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-49 years</td>
<td>≥ 7.0</td>
<td>≥ 1.10</td>
</tr>
<tr>
<td>50-64 years</td>
<td>≥ 5.0</td>
<td>≥ 1.05</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>≥ 3.5</td>
<td>≥ 1.00</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-49 years</td>
<td>≥ 9.0</td>
<td>≥ 1.10</td>
</tr>
<tr>
<td>50-64 years</td>
<td>≥ 6.0</td>
<td>≥ 1.05</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>≥ 4.0</td>
<td>≥ 1.00</td>
</tr>
</tbody>
</table>

* Measured one minutes after termination, †Does not equal values from full blood analysis, \(L\) = litre, \(\text{RER}\) = Respiratory Exchange Ratio, \(\dot{V}O_2\) = Oxygen uptake, \(\dot{V}CO_2\) = Carbon dioxide output.
5.3 paper III

Change in cardiorespiratory fitness after lung cancer surgery is not related to the amount of lung tissue removed

The objective was to evaluate the effect of lung cancer surgery on CRF measured on a treadmill, and to assess the agreement between the predicted postoperative (ppo) and actually measured postoperative peak oxygen uptake ($\dot{V}O_2\text{peak}$).

1. Prior to surgery the $\dot{V}O_2\text{peak}$ was 23.2 ± 5.6 mL·kg$^{-1}$·min$^{-1}$ in women and 24.6 ± 5.9 mL·kg$^{-1}$·min$^{-1}$ in men, which was 84 and 76 % of predicted, respectively. The $\dot{V}O_2\text{peak}$ was impaired in 56 % of the patients ($\dot{V}O_2\text{peak} < 80 \%$ of predicted).

2. After surgery, the $\dot{V}O_2\text{peak}$ decreased by 17.4 ± 14.4 % ($P < 0.001$) and 33.6 ± 17.9 % ($P < 0.001$) in those who underwent lobectomy and pneumonectomy, respectively. Furthermore, the FEV$\text{}_{1}$ decreased by -17.7 ± 17.1 % ($P < 0.001$), the DL$\text{CO}$ decreased by -20.1 ± 14.0 % ($P < 0.001$), the breathing reserve increased by 5.3 ± 11.1 % ($P = 0.001$), the oxygen saturation remained unchanged ($P = 0.30$), the O$_2$ pulse decreased by -12.7 % ($P < 0.001$) and the haemoglobin decreased by -4.4 % ($P = 0.001$).

3. The strongest independent association between per cent change in physiological variables after surgery and per cent change in $\dot{V}O_2\text{peak}$ was found for the O$_2$ pulse; adjusted simple squared $r^2 = 0.756$. Adding change in FEV$_{1}$, DL$\text{CO}$, MVV, breathing reserve, oxygen saturation at peak exercise and haemoglobin did not add any noticeable predicting value; adjusted $r^2 = 0.826$.

4. In the non-exercising patients ($n = 23$), the $\dot{V}O_2\text{peak}$ decreased nonsignificantly from after surgery to six month after surgery (-3 ± 15 %, $P = 0.27$).

5. There were no significant differences between the ppo and actually measured values (satisfactory accuracy) (Table 8, page 40). However, the segment method miscalculated the ppo $\dot{V}O_2\text{peak}$ by more than ± 10 and ± 20 % in 54 % and 25 % of the patients, respectively (Figure 2,
The accuracy, agreement and linear correlation between predicted postoperative variables for FEV$_1$, DL$_{CO}$ and $\dot{V}O_2$peak are presented in Table 8.

Table 8. Predicted postoperative (ppo) values and actually measured 4-6 weeks after surgery for pulmonary function (n=63) and peak oxygen uptake (n=59).

<table>
<thead>
<tr>
<th>ppo value</th>
<th>Actually measured after surgery</th>
<th>Difference ppo-measured</th>
<th>P-value</th>
<th>Limits of Agreement</th>
<th>Linear correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV$_1$ (% pred)</td>
<td>69.5 ± 19.9</td>
<td>72.9 ± 17.5</td>
<td>-3.4 ± -13.7</td>
<td>0.06</td>
<td>-23.5 to 30.2</td>
</tr>
<tr>
<td>DL$_{CO}$ (% pred)</td>
<td>63.6 ± 18.9</td>
<td>65.4 ± 18.1</td>
<td>-1.7 ± -12.3</td>
<td>0.27</td>
<td>-22.3 to 25.8</td>
</tr>
<tr>
<td>$\dot{V}O_2$peak (% pred)</td>
<td>63.1 ± 16.5</td>
<td>65.4 ± 16.9</td>
<td>-2.3 ± -13.3</td>
<td>0.20</td>
<td>-23.8 to 28.3</td>
</tr>
<tr>
<td>$\dot{V}O_2$peak (mL·kg$^{-1}$·min$^{-1}$)</td>
<td>18.6 ± 5.4</td>
<td>19.2 ± 5.5</td>
<td>-0.6 ± -4.1</td>
<td>0.24</td>
<td>-7.4 to 8.7</td>
</tr>
</tbody>
</table>

* Linear correlation is significant at the 0.01 level

DL$_{CO}$=carbon monoxide lung diffusion capacity, FEV$_1$=forced expiratory volume after one second, n = number, $\dot{V}O_2$peak = peak oxygen uptake;
5.4 Paper IV

*High-Intensity training following lung cancer surgery: a randomised controlled trial*

In this trial, the effects of high-intensity endurance- and progressive resistance training were evaluated on $\dot{V}O_{2\text{peak}}$, pulmonary function, maximum strength, functional fitness, total muscle mass and QoL.

1. The intention-to-treat analysis showed that the exercise group had greater increase in $\dot{V}O_{2\text{peak}}$ (3.4 mL·kg$^{-1}$·min$^{-1}$ or 18.9 % between-group difference, $P = 0.002$), compared with the control group.

2. The per-protocol analysis showed a between-group difference between the exercise group and the control group of 5.0 mL·kg$^{-1}$·min$^{-1}$ or 30.3 % ($P < 0.001$).

3. The exercise group also improved in DL$\text{CO}$ (5.2 % predicted, $P = 0.007$), 1RM leg press (29.5 kg, $P < 0.001$), chair stand (2.1 times $P < 0.001$), stair run (4.3 steps, $P = 0.002$), and total muscle mass (1.36 kg, $P = 0.012$) compared with the control group. No significant differences in balance were found between the groups ($P = 0.33$).

4. The *Physical component summary score* and the *Mental component summary score* in SF-36 were significantly higher in the exercise group compared to the control group after the training intervention; 51.8 ± 5.5 vs 43.3 ± 11.3 ($P = 0.006$) and 55.5 ± 5.3 vs 46.6 ± 14.0 ($P = 0.02$), respectively. Correspondingly, the dyspnoea score in the EORTC QOL-C30 was lower in the exercise group compared to the control group after the intervention; 37.0 ± 25.3 vs 58.0 ± 32.1, respectively ($P = 0.03$).

5. High-intensity endurance- and strength training was well tolerated. However, all patients receiving chemotherapy had to postpone their training sessions until they had completed the treatment.
6.0 GENERAL DISCUSSION

The current thesis presents normative reference values gathered during CPET to maximum on a treadmill (paper I), and provides new recommendations for end criteria for determining that a subject has reached a maximum effort during an exercise test (paper II). In NSCLC patients, $\dot{V}O_{2\text{peak}}$ was impaired before surgery in 56% of the patients and decreased significantly after surgery by an average of 20% (paper III). However, predicting the postoperative $\dot{V}O_{2\text{peak}}$ based on the number of segments removed had poor precision and was thus not valid. A high-intensity endurance- and strength training program counteracted the decline in $\dot{V}O_{2\text{peak}}$ and even increased it to a level higher than that before surgery in more than half of the patients (paper IV).

This part of the thesis discusses the most important findings in the context of the recently published literature.

6.1 Cardiorespiratory fitness

The $\dot{V}O_{2\text{max}}$ in the 20-29-year-old Norwegian population was $40.3 \pm 7.1 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in women and $48.6 \pm 9.6 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in men, and declined linearly by 8% per decade after the age of 30 years. These levels are higher than those reported in similar studies from Canada,\textsuperscript{108,112} the United States,\textsuperscript{118,143} and Israel,\textsuperscript{111} but significantly lower than those reported in the Norwegian HUNT Fitness Study\textsuperscript{121,122} (Figures 11 and 12, page 43 og 44). In 2011, Aspenes and coworkers reported $\dot{V}O_{2\text{peak}}$ data from an impressive large sample of 4,631 healthy men and women aged 20–90 years. The data were collected between October 2006 and June 2008, and all participants exercised on a treadmill until voluntary exhaustion. The $\dot{V}O_{2\text{peak}}$ was about 10% higher in all age cohorts and both sexes compared with the values in the present study despite the fact that we used a strict end criterion for $\dot{V}O_{2\text{max}}$, in contrast to the study by Aspenes and coworkers who used no end criterion. In addition, the HRmax was slightly higher in the HUNT Fitness Study (by ~3.5 beats min$^{-1}$), as recently reported by Loe and coworkers.\textsuperscript{144} Conversely, the $\dot{V}E$ was similar and the RER was significantly lower in all age cohorts compared with the present study. Moreover, Loe and coworkers published another set of $\dot{V}O_{2\text{max}}$ reference variables derived from the same HUNT Fitness Study dataset after excluding the 815 participants who did not exhibit a leveling off in VO$_2$ as shown by an increase of > 2 mL·kg$^{-1}$·min$^{-1}$.\textsuperscript{122} Consequently, 52% of the participants in the eldest age cohort were excluded. Hence, the difference between the latest HUNT Fitness Study results and ours increased in the
eldest age cohorts. To summarise, the HUNT Fitness Study has reported the highest $\dot{V}O_2$peak and $\dot{V}O_2$max data ever for all age cohorts and both sexes compared with similar population studies. The difference is about 15% in the eldest age cohort, compared to our data, after excluding those who did not achieve a leveling off in VO$_2$.

To explain the differences between the two Norwegian studies conducted at the same time and in the same country, it has been argued that the health status differed between our population and the participants in the HUNT Fitness Study. However, the absolute difference in $\dot{V}O_2$max values between the studies was fairly consistent across age strata (Figures 11 and 12, page 43 and 44), implying that the health aspect may be less important. Other causes may be related to differences in activity levels, recruitment strategies, exclusion criteria, and technical aspects such as the use of stationary (three types) versus mobile gas analyzers.

Figure 11. Population based measurement of peak- or maximal oxygen uptake in healthy men related to age.
6.1.1 Choice of reference values

The availability of normative reference values is limited, especially in elderly women, which highlights the importance of updating the reference values. The choice of reference values when calculating the percent predicted values is, however, a challenging task, and many factors must be considered such as the population included, age and sex, mode of exercise used, variables included, and physical activity level. According to our reference values, the average $\dot{V}O_{2\text{peak}}$ in the present lung cancer patients was 80 % ± 17 % of predicted. When applying the reference values from Loe et al., the $\dot{V}O_{2\text{peak}}$ in percent of predicted was reduced to 68 ± 15 % of predicted. The ERS/ESTS guidelines recommend a cutoff limit of >35 % of ppo $\dot{V}O_{2\text{peak}}$ for accepting patients for surgery (Figure 4, page 12). Using the reference values from the HUNT Fitness Study would have meant that eight patients (11 %) in our study would have been rejected for surgery, which could have had a serious impact on the prognosis of these patients. However,
this argument still does not provide a clear answer about which reference values to choose. The HUNT Fitness Study has an impressively large sample size covering all ages and both men and women, which increases its credibility. In contrast to the results published from the HUNT Fitness Study, the present reference values were derived from tests that included the most common exercise variables used when interpreting CPET. These were measured during a continuous graded exercise test and also included measures of pulmonary function, BP and blood lactate concentration. In addition, the participants’ activity levels were objectively measured by accelerometers. However, which one to be used is up to other to judge.

6.2 End criteria for determining that maximal oxygen uptake is achieved

There is at present no consensus regarding the criteria for ensuring that a maximum effort is achieved during exercise testing, especially among women and the elderly. The standards used have either been too low, too high, or not specified, which may increase the likelihood of underestimating or overestimating $\dot{V}O_{2\text{max}}$. This makes it difficult to compare different populations and to accurately assess patient outcomes based on clinical exercise testing. Consequently, we have presented new end criteria recommendations for $\dot{V}O_{2\text{max}}$ (Table 7, page 38) using the RER and postexercise blood lactate concentration based on age and sex differences derived from the original database. A high RER during maximum effort indicates a high level of anaerobic metabolism and has traditionally been the most-used secondary criterion for determining that $\dot{V}O_{2\text{max}}$ has been achieved if there is no leveling off of $\dot{V}O_{2}$. In addition, RER is easy to supervise during and at the end of the test, which may be important in terms of the motivation and assessment of patient effort. However, RER may be influenced by the individual’s breathing pattern, in contrast to the lactate concentration, which is a variable that cannot be manipulated, is easy to measure, and has high measurement accuracy. Thus, including lactate concentration in the recommendation gives a more objective reflection of exercise intensity.

One reason why we did not use the classical leveling-off definition described by Taylor and coworkers was because the continuous graded exercise protocol typically used during CPET may lead to the appearance of several $\dot{V}O_{2}$ plateaus during the test, which may preclude the recording of a valid $\dot{V}O_{2\text{max}}$ (Figure 9, page 29). This is particularly important during clinical exercise testing using a continuous
graded exercise protocol or when testing elderly frail individuals. A “true” leveling off was achieved in only 42% of the participants in paper II.

6.2.1 End-criteria for determining that $\dot{V}O_{2\text{max}}$ has been achieved in NSCLC patients

Because of severe obstruction, COPD patients may exhibit ventilatory limitations before the cardiovascular system has reached its maximum capacity, which would lead to less reliance on anaerobic metabolism during exercise, and thereby lower RER and lactate concentration compared with patients with cardiovascular disease and healthy individuals. It is reasonable to assume that this is also the case for lung cancer patients with COPD, whose limited exercise capacity because of impairments in ventilatory mechanics may increase after surgery. Thus, it is not surprising that, before surgery, 16 lung cancer patients did not fulfill our recommendation for determining that a maximum effort had been achieved, even though most patients knew upfront that a poor outcome would exclude them from life-saving treatment, which should have motivated them to maximal effort. However, these patients had some important characteristics such as significantly higher smoking pack-years (42 vs 24), lower DLCO (71% vs 83% predicted), higher $V_{E}/\dot{V}CO_{2}$ (35 vs 32), lower peak HR (132 vs 148 beats $\cdot$ min$^{-1}$), and lower cardiorespiratory fitness ($\dot{V}O_{2\text{peak}}$ of 67% vs 83% predicted). In other words, these patients had a poorer health status compared with those who fulfilled the end criteria. Unexpectedly, ventilatory function did not contribute to exercise limitations because the patients had an average breathing reserve of 35%, which excludes the “COPD argument” discussed previously. Taken together, our results show that some NSCLC patients cannot stress their cardiovascular system to maximum effort and thus fail to meet our recommendations, probably because of their poor health and physical condition and not because of limited ventilatory mechanics.

The lower RER and blood lactate accumulation in these patients may also be explained by dyspnea (which is common in these patients), loss of type II skeletal muscle fibers, and a lower capacity for anaerobic glycolysis. Nevertheless, maximum effort is still essential for meeting the guidelines’ recommended criteria for surgery, and it is thus important to motivate the patient as much as possible during CPET. Several recent lung cancer investigations seem to have a low requirement regarding maximum effort during CPET. This is reflected by the markedly lower peak HR and $\dot{V}O_{2\text{peak}}$ values compared with those of Norwegian NSCLC patients, even though the age, body mass, pulmonary function, and percentages of patients with comorbidities were comparable with those of...
other NSCLC populations. Thus, we recommend that typical end criteria variables for determining that $\dot{V}O_{2\text{peak}}$ has been achieved should be reported in future studies to allow comparisons between studies and between populations.

After surgery, 36 patients (56 %) did not fulfill our recommendations for criteria for determining that a maximum effort was achieved, even though the rating on the Borg scale was slightly higher (17.6 vs 17.3). Furthermore, the breathing reserve increased significantly, indicating no ventilatory limitation, even though a substantial amount of lung tissue had been removed in most patients. One reason for the lower ability to exert a maximum effort after surgery may relate to the significant loss of muscle mass, especially in the upper body/torso (data not shown). This loss of muscle mass may cause fatigue in the respiratory muscles at an earlier stage, thus increasing the feeling of dyspnea. Further investigations are required to address this question fully.

### 6.3 Cardiorespiratory Fitness in the Lung Cancer Patient

CPET with measurement of $\dot{V}O_{2\text{peak}}$ has been examined extensively in lung resection candidates, and several studies have concluded that a low preoperative $\dot{V}O_{2\text{peak}}$ relative to body mass is associated with a high risk of cardiopulmonary complications. In addition, evidence for a relationship between cardiorespiratory fitness and survival has increased, and there is a strong association between cardiorespiratory fitness and survival.

#### 6.3.1 Peak Oxygen Uptake Prior to Surgery – Method a Challenge?

In the FALC population, the $\dot{V}O_{2\text{peak}}$ was 23.6 ± 6.0 mL·kg\(^{-1}\)·min\(^{-1}\) before surgery and ranged from 11.4 to 45.3 mL·kg\(^{-1}\)·min\(^{-1}\) (43–116 % of predicted). Despite an impaired $\dot{V}O_{2\text{peak}}$ in 56 % of the patients, the cardiorespiratory fitness level was clearly higher compared with other populations reported from Italy, Switzerland, the United Kingdom, North America, and Japan. The high cardiorespiratory fitness level may indicate fewer cardiopulmonary complications compared with other populations given the association between $\dot{V}O_{2\text{peak}}$ and the risk of surgery. However, this was not the case; 20 patients in the Norwegian population exhibited 24 moderate to severe cardiopulmonary complications including three deaths (data not previously shown), which is similar to other reports.
Hence, we do not have any indications that our Norwegian lung cancer patients are more fit than other NSCLC populations, and the age, pulmonary function, and percentage of patients with comorbidities and cardiopulmonary complications were similar to those of other NSCLC populations. Thus, one may speculate that the higher \( \dot{V}O_{2\text{peak}} \) in our population reflects the exercise mode used. All studies mentioned above used cycle ergometry, in contrast to the use of uphill walking on a treadmill in our study. Uphill walking is common, a more functional and dynamic exercise mode compared with cycling and involves greater activation of more muscle mass because of the increased recruitment of the quadriceps muscle. Simultaneously, it generates lower blood pressure and blood lactate accumulation, and a higher cardiac output, which contribute to a 10–20 % higher \( \dot{V}O_{2\text{peak}} \). It is thus surprising that only a limited number of studies have used CPET on a treadmill ergometer when categorizing risk for patients being screened for NSCLC surgery. We therefore recommend treadmill testing for preoperative measurement of \( \dot{V}O_{2\text{peak}} \) in these patients in future.

### 6.3.2 Sex differences and risk stratification

\( \dot{V}O_{2\text{max}} \) relative to body weight (mL·kg\(^{-1}\)·min\(^{-1}\)) was significantly lower by ~20 % in healthy women compared with healthy men (paper I), which is consistent with the results from the HUNT Fitness Study. By contrast, there was no significant sex difference in \( \dot{V}O_{2\text{peak}} \) in the NSCLC patients in this study. When expressed as a percentage of the predicted value, \( \dot{V}O_{2\text{peak}} \) was in fact 11 % higher in women even though the age span and pulmonary function were similar in men and women. These differences may be one reason why there were fewer cardiopulmonary complications after surgery in the women (three women with complications) than in the men (17 men with complications) (data not shown). This sex difference has not been taken into consideration in the latest guidelines. Thus, the demand to achieve an acceptable \( \dot{V}O_{2\text{peak}} \) during risk stratification is more difficult for women, even though the incidence of complications is lower. This might suggest that future guidelines should focus more on the percentage of predicted \( \dot{V}O_{2\text{peak}} \) rather than absolute value, which is similar to the guideline recommendations for FEV\(_1\) and DL\(_{CO}\). Further investigation should address this question fully.
6.3.1 Agreement between predicted and observed variable

One major procedure in all preoperative guidelines for lung cancer surgery is the split-function technique using the segment method to predict postoperative pulmonary function.\textsuperscript{1,7,81} This method is based on the principle that the number of resected functional lung segments corresponds to the loss of FEV\textsubscript{1} and DL\textsubscript{CO}.\textsuperscript{1,7,81} However, the correlation between the ppo and actually measured FEV\textsubscript{1} is variable, and the r-values previously reported range from 0.67 to 0.9.\textsuperscript{1} Moreover, the ERS/ESTS guidelines also include ppo $\dot{V}O_{2\text{peak}}$ in the algorithm, despite the fact that $\dot{V}O_{2\text{peak}}$ is generally limited more by cardiac output than by pulmonary function.\textsuperscript{29} Based on the interpretation of the change in pulmonary function and the results of CPET in the present thesis, we support the concept that a reduction in $\dot{V}O_{2\text{peak}}$ seems to reflect a reduction in cardiac function, and not by a decrease in pulmonary function after resection in NSCLC patients. Furthermore, we found that although the calculation of ppo $\dot{V}O_{2\text{peak}}$ was quite accurate, the precision was poor. This was also the case for FEV\textsubscript{1} and DL\textsubscript{CO} (Table 8, page 40). Thus, the prediction of postoperative FEV\textsubscript{1}, DL\textsubscript{CO}, and $\dot{V}O_{2\text{peak}}$ from the number of lung segments removed should be questioned.

6.4 Effects of Surgery

Consistent with other investigations,\textsuperscript{9} the $\dot{V}O_{2\text{peak}}$ decreased significantly 4–6 weeks after surgery. The largest decrease occurred in those patients who underwent a pneumonectomy. However, the correlation between the reduction in $\dot{V}O_{2\text{peak}}$ and amount of lung segments removed was low. In addition, most patients had an excellent ventilatory reserve after surgery, and the SpO\textsubscript{2} during maximum exercise was unchanged, even though DL\textsubscript{CO} decreased significantly. We found that the $O_2$ pulse was the strongest predictor of a change in $\dot{V}O_{2\text{peak}}$. Hence, adding the changes in FEV\textsubscript{1}, MVV, breathing reserve, DL\textsubscript{CO}, SpO\textsubscript{2}, and Hb concentration to the multiple regression models resulted in only a modest increase in the predictive value.

Not surprisingly, the feeling of dyspnea increased after surgery, even though the breathing reserve increased significantly. The increased dyspnea despite the greater breathing reserve may be caused by the increased work of breathing, which is the case after lung cancer surgery.\textsuperscript{155} This could divert a greater proportion of oxygenated blood from the muscles of locomotion to the muscles of ventilation, and thus lead to early exhaustion during exercise. If so, $\dot{V}O_{2\text{peak}}$ should not be affected, but the feeling of dyspnea...
may be increased because of the increased oxygen cost in the ventilatory muscles. We found a clinically significant loss of muscle mass in the trunk after surgery, as measured by dual-energy x-ray absorptiometry (data not shown), which might have exacerbated the feeling of dyspnea. There was also a clinically and statistically significant loss of total muscle mass and muscular strength from before to after surgery (Figure 2, paper IV). We have not found other investigations of the changes in muscle mass and muscular strength from before to after surgery.

In the nonexercising patients who underwent testing 6 months after surgery (n = 23), FEV1 increased significantly by 7 %, whereas DLCO, \( \dot{V}O_{2\text{peak}} \), and 1 RM in leg press strength remained unchanged compared with the measurements performed 4–6 weeks after surgery (papers III and IV). Given the large effects of surgery on the loss of cardiorespiratory fitness, muscular strength, and total muscle mass, it seems logical to focus on early mobilization and exercise rehabilitation after surgery.

6.5 Effects of exercise

Before the start of data collection in this thesis, only three studies had examined the effects of exercise in patients undergoing lung resection.97,101,102 As mentioned in the introduction/background section none of these used a randomised design, and only one study by Jones and coworkers measured \( \dot{V}O_{2\text{peak}} \) directly by gas exchange.97 Jones and coworkers assessed the effects of a training program and focused on increasing \( \dot{V}O_{2\text{peak}} \) using a single-group design. Nineteen patients completed the study, which comprised three aerobic sessions per week for 14 weeks on a bicycle ergometer. Despite excellent adherence to exercise training, intention-to-treat analysis showed a nonsignificant increase in \( \dot{V}O_{2\text{peak}} \) by 1.1 mL·kg\(^{-1}\)·min\(^{-1}\). This was despite the fact that the participants were younger and had better pulmonary function and a lower \( \dot{V}O_{2\text{peak}} \) compared with the patients included in this thesis, which makes the negative results somewhat surprising. However, there are some important factors that may explain the discrepancy between the results. First, the intervention in our study had greater total work performed/strain during the intervention, and a 4-week longer intervention period. Second, the mode of endurance training differed between the studies. Third, FALC included progressive resistance training in the intervention, which was not included in the study by Jones but may have contributed to a greater increase in \( \dot{V}O_{2\text{peak}} \) in the study presented in the current thesis. It is known that resistance training can increase \( \dot{V}O_{2\text{peak}} \), especially in severely deconditioned adults.49,156
Four RCTs have been published recently (Table 3, page 17). The results of these studies are conflicting and these studies could not document positive training effects. This could probably be due to short interventions, poorly maintained or low exercise intensity, home-based programs without clearly established follow-ups, and the lower quality of methodology used for the measurements. For instance, the mode of exercise used in the test to evaluate training effects differed from that used in exercise training during the intervention, which contradicts the principle of test specificity. Given the clinical importance of cardiorespiratory fitness, it is surprising that none of these RCTs measured \( \dot{V}O_{peak} \). The net increase in \( \dot{V}O_{peak} \) of 3.4 mL·kg\(^{-1}\)·min\(^{-1}\) in the present thesis using intention-to-treat analysis or as much as 5.0 mL·kg\(^{-1}\)·min\(^{-1}\) using per-protocol analysis is quite high compared with other cancer survivors. This is despite the fact that the patients had higher prevalence of COPD and heart disease, and had recently undergone major surgery affecting their ability to move and breathe. In general, an increase in \( \dot{V}O_{peak} \) of 3.5 mL·kg\(^{-1}\)·min\(^{-1}\) corresponds to a 12–17 % improvement in survival rate, and \( \dot{V}O_{peak} \) is a strong and independent predictor of survival, also in NSCLC patients.

In a recent meta-analysis, Strasser and coworkers demonstrated that the pooled effect of resistance training on lower-limb muscular strength was a significant mean increase of 14.6 kg (95 % CI = 6.34–22.8 kg) in adult cancer survivors. In the present study, the net increase in 1 RM leg press strength was 29.5 kg, and the overall increase in total muscle mass was 1.36 kg, indicating strong positive effects after progressive resistance training in our patients. Taken together, the present RCT has demonstrated that NSCLC patients could perform high-intensity endurance and strength training shortly after major lung cancer surgery. Such training seems to be necessary in the NSCLC population if the goal is to increase both \( \dot{V}O_{peak} \) and muscle strength. High-intensity endurance and strength training may hold considerable promise for improving the prognosis of NSCLC patients. Knowing that lung resection has both direct (lungs and blood) and indirect (heart and muscles) effects on vital organs, clinicians and health providers should encourage patients to improve cardiorespiratory fitness and skeletal muscle strength to increase their physical fitness after lung resection. Increasing fitness and strength will help them recover more quickly after treatment, increasing the QoL, and prevent late side effects.
6.6 Representativeness

The decreasing response rates in most of today’s randomly selected surveys may be a challenge and a major concern, and several studies have shown that non-respondents differ from respondents in their health profiles and socioeconomic status. The subjects in paper I and II all participated in an initial survey wearing accelerometers. They were drawn from the Norwegian population registry, and were randomly selected throughout Norway from the areas surrounding each test center. The participation rate after telephone contact from the originally invited population was 66%. Given that all the participants had to come to the examination during the day, and several had to travel quite long distances, the participation rate seems high. Nevertheless, a comprehensive nonresponse analysis was undertaken, and showed that there was a clear selection bias insofar as the respondents had a higher educational status than the nonrespondents. Therefore, the participants in paper I and II may have had better health and consequently greater cardiorespiratory fitness than the nonrespondents.

Regarding the NSCLC patients, the baseline characteristics are representative for the lung cancer population undergoing surgery, both regarding age, gender, pulmonary function, histology, comorbidities, and use of adjuvant therapy. However, the $\text{VO}_2\text{peak}$ was clearly higher than previously reported. This may be explained by the use of uphill treadmill walking instead of bicycling during CPET, and also higher effort. This is further discussed in chapter 6.3.1.
7.0 Strength and limitations

7.1 Part I – Healthy population

The main strengths in paper I and II were its large and well-described sample of men and women, their random inclusion from rural and urban populations, and the wide age range. Furthermore, the end criteria used for $\dot{V}O_{2}\text{peak}$ in paper I were rather strict compared with those of other studies.\textsuperscript{105,108-111,115}

The limitations in part I were the use of nine different test laboratories, including three different gas analyzer models, which may have increased the possibility of different test methods and measurement accuracies across the test laboratories. However, some initiatives were taken to minimize these differences. First, all the technicians were rigorously trained in all test procedures and they were experienced with maximal exercise testing. Second, all the gas analyzers were calibrated to an artificial lung. Unfortunately, we detected some differences in the degree of motivating the participants between the test laboratories. This finding underlines the importance of paper II, which goal is to increase the quality and validity between future studies and test laboratories.

7.2 Part II – NSCLC patients

Strength of paper III and IV are directly measurements of $\dot{V}O_{2}\text{peak}$, involving equal amount of men and women, and the use of uphill walking during the CPET instead of cycling. In paper IV, we included high-intensity training in community fitness centers using personal trainers with one-on-one supervision individually tailored. This design made it possible to ensure individual exercise progressions from week to week. In addition, the training duration of 20 weeks was quite long. Finally, our dropout rate was low compared with the expected rate in both groups.

There are also some limitations. In paper III, we did not measure stroke volume during exercise to verify the conclusions based on findings from the $O_2$ pulse. Normally, a low $O_2$ pulse reflects cardiac limitation if the patient does not desaturate.\textsuperscript{2,147} To confirm the impact on cardiac limitation, we in retrospect calculated the change in the patients’ stroke volume by estimating the arteriovenous oxygen difference,\textsuperscript{2,69} finding a 10 % reduction in the stroke volume ($P < 0.001$) from before to after surgery (data not shown).
A methodological limitation in the RCT (paper IV) was a low response rate to the QoL questionnaires, probably related to too many questions. Furthermore, we cannot rule out the possibility that the technicians were not blinded during the last data collection. However, end criteria for maximal effort did not differ between the groups, neither before randomization nor after, confirming no different effort between the groups.
8.0 CONCLUSIONS

Part one of this thesis gave recommendations for new reference values during CPET on a treadmill and end criteria for maximal testing. Part two investigated changes in cardiorespiratory fitness after lung cancer resection, and studied the effect of a high-intensity endurance and strength training program. We believe that the following clinical findings are justified:

**Paper I**: Results from a large and well-described population were presented regarding different maximal cardiorespiratory fitness variables for men and women on a treadmill across all ages from 20-to 85 years. In the 20- to 29-year-old age group, $\dot{V}O_{2\text{max}}$ (mL·kg$^{-1}$·min$^{-1}$) was 40.3 ± 7.1 in women and 48.6 ± 9.6 in men. A linear decline (8 % per decade) was observed after age 30 years in both sexes. Maximal HR decreased with age by ± 6.3 beat/min per decade. The maximal $O_2$ pulse was 33 % lower in women and decreased significantly with age in both sexes. Women's maximal ventilation was 66 % that of men and decreased with age after 40 to 49 years in both sexes. The breathing reserve was higher in women than in men. This study established reference values for $\dot{V}O_{2\text{max}}$, maximal HR, $O_2$ pulse, BP, ventilation, breathing reserve, respiratory exchange ratio, and blood lactate concentration during maximal exercise on treadmill.

**Paper II**: A range of maximal end criteria were presented in a random sample of healthy men and women aged 20-to 85 years. Forty-two percent of the participants achieved a plateau in VO$_2$ at the end of the test. There were no sex-related differences in HR$_{\text{max}}$, RER, or BORG Scale rating, whereas blood lactate concentration was 18 % lower in women. When using RER $\geq$ 1.15 or blood lactate concentration $\geq$ 8.0 mmol·L$^{-1}$, $\dot{V}O_{2\text{max}}$ was 4 % and 10 % greater, respectively. A blood lactate concentration $\geq$ 8.0 mmol·L$^{-1}$ excluded 63 % of the participants in the 50-85-year-old cohort. Thus, the choice of end criteria during exercise testing had an impact on sex and the number of participants, and some impact on the outcome of the test. Based on these results, new recommendations were given according to age and sex for individuals using a continuous graded exercise protocol on a treadmill.
CONCLUSIONS

Paper III: The effect of lung cancer surgery was evaluated regarding maximal cardiorespiratory fitness variables, and the agreement between the predicted postoperative and actually measured $\dot{V}O_{2\text{peak}}$ were presented. The marked reduction in $\dot{V}O_{2\text{peak}}$ after lung cancer surgery was significant, and did not improve during six months. The reduction seemed to be caused by a decrease in the patients’ cardiac function, and not by reduced pulmonary function. Predicting postoperative $\dot{V}O_{2\text{peak}}$ based on the amount of lung segments removed appears not to be recommendable due to poor precision. Predicting postoperative $\dot{V}O_{2\text{peak}}$ based on the number of lung segments removed showed poor precision when compared with actually measured postoperative $\dot{V}O_{2\text{peak}}$.

Paper IV: A randomised controlled supervised high-intensity endurance- and strength training was performed in lung cancer patients shortly after surgery. Compared with standard postoperative care, high-intensity endurance and strength training was well tolerated and induced clinically significant improvements in $\dot{V}O_{2\text{peak}}$, DLCO, muscular strength, total muscle mass, functional fitness and quality of life.
9.0 IMPLICATIONS

Paper I
Cardiopulmonary exercise tests are commonly used to study an individual’s cardiorespiratory fitness. There is today limited knowledge about reference values for $\dot{V}O_{2\text{max}}$ and other cardiorespiratory fitness variables typical used during a CPET, especially for women and elderly. This study gives new reference values for both men and women age 20- to 85-years, covering the most important variables used in a clinical setting during maximal effort.

Paper II
This study will have an impact on clinical practice regarding an increased focus on standardised methods for reaching and for documenting maximal effort during performance- and during clinical exercise testing. Technicians, physicians and researchers should more confidently be able to evaluate the degree of maximal effort during a progressive incremental exercise test, and thereby increase the quality and validity of the test.

Paper III
This study gives important information about the impact lung cancer surgery has on the cardiorespiratory fitness and its reasons, and that the postoperative $\dot{V}O_{2\text{peak}}$ is difficult to predict at an individual basis. Based on the interpretation of the results, the segment method for predicting postoperative $\dot{V}O_{2\text{peak}}$ is not recommendable. Physicians and health care workers should as early as possible mobilise the patient after surgery avoiding inactivity and thereby loss in cardiac output.

Paper IV
Based on our positive results, and that high-intensity endurance- and strength training were well tolerated shortly after surgery, this study might have an impact on future post-operative care of lung cancer patients, making them recover quicker after surgery. Given the positive prognostic value of improving exercise capacity from other studies,\textsuperscript{4,5,48} and findings in the present study, clinicians and health allied should encourage lung cancer patients to improve their CRF and muscular strength, preferably as soon as possible after recover from surgery.
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Paper I
Cardiopulmonary exercise testing (CPET) is a common and reliable noninvasive measure of the cardiac and respiratory responses during incremental exercise. At rest and during exercise, several physiologic variables are measured, including pulmonary function, ventilatory response, pulmonary gas exchange, BP, ECG, and maximal oxygen uptake (VO\textsubscript{2 max}). Thus, CPET quantitates an individual’s exercise capacity and provides valuable diagnostic and prognostic information about the cardiorespiratory system.\textsuperscript{1} It is also a useful predictor of postoperative complications after pulmonary resection surgery\textsuperscript{2} and in assessing the timing of cardiac transplant surgery.\textsuperscript{3}

To interpret the results of CPET, normative reference values are required. Reference values have been derived from small nonrandom samples, lacking women and older individuals and some with poor or no maximal end criteria. The objective was to study the cardiorespiratory response during maximal exercise in a representative predominantly Caucasian sample of men and women.

Methods: Nine hundred four randomly sampled men and women, 20 to 85 years old, exercised on a treadmill to exhaustion. Oxygen uptake (VO\textsubscript{2}), heart rate (HR), BP, lactate concentration, and ventilatory variables were measured.

Results: Seven hundred fifty-nine participants met the criteria for an acceptable maximal VO\textsubscript{2} (VO\textsubscript{2 max}) based on a respiratory exchange ratio \textsuperscript{11} or a Borg score \textsuperscript{17}. In the 20- to 29-year-old age group, VO\textsubscript{2 max} (mL/kg/min) was 40.3 (± 7.1) in women and 48.6 (± 9.6) in men. A linear decline (8% per decade) was observed after age 30 years in both sexes. Maximal HR decreased with age by ± 6.3 beats/min per decade. The maximal oxygen pulse was 33% lower in women and decreased significantly with age in both sexes by 5% and 3% per decade for women and men, respectively. Women’s maximal ventilation was 66% that of men and decreased with age after 40 to 49 years in both sexes. Breathing reserve was higher and blood lactate was lower in women than in men.

Conclusions: This study establishes reference values for VO\textsubscript{2 max} (absolute, relative to body weight and fat-free weight), maximal HR, oxygen pulse, BP, ventilation, breathing reserve, respiratory exchange ratio, and blood lactate concentration during maximal exercise on treadmill in a large population.

Abbreviations: CPET = cardiopulmonary exercise test; FFM = fat-free mass; HR = heart rate; HRmax = maximal heart rate; MVV = maximal voluntary ventilation; RER = respiratory exchange ratio; V\textsuperscript{E}max = maximal minute ventilation; VO\textsubscript{2 max} = maximal oxygen uptake.

Reference Values for Cardiorespiratory Response and Fitness on the Treadmill in a 20- to 85-Year-Old Population

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Background: Existing reference values for clinical exercise testing have been derived from small nonrandom samples, lacking women and older individuals and some with poor or no maximal end criteria. The objective was to study the cardiorespiratory response during maximal exercise in a representative predominantly Caucasian sample of men and women.

Methods: Nine hundred four randomly sampled men and women, 20 to 85 years old, exercised on a treadmill to exhaustion. Oxygen uptake (VO\textsubscript{2}), heart rate (HR), BP, lactate concentration, and ventilatory variables were measured.

Results: Seven hundred fifty-nine participants met the criteria for an acceptable maximal VO\textsubscript{2} (VO\textsubscript{2 max}) based on a respiratory exchange ratio \textsuperscript{11} or a Borg score \textsuperscript{17}. In the 20- to 29-year-old age group, VO\textsubscript{2 max} (mL/kg/min) was 40.3 (± 7.1) in women and 48.6 (± 9.6) in men. A linear decline (8% per decade) was observed after age 30 years in both sexes. Maximal HR decreased with age by ± 6.3 beats/min per decade. The maximal oxygen pulse was 33% lower in women and decreased significantly with age in both sexes by 5% and 3% per decade for women and men, respectively. Women’s maximal ventilation was 66% that of men and decreased with age after 40 to 49 years in both sexes. Breathing reserve was higher and blood lactate was lower in women than in men.

Conclusions: This study establishes reference values for VO\textsubscript{2 max} (absolute, relative to body weight and fat-free weight), maximal HR, oxygen pulse, BP, ventilation, breathing reserve, respiratory exchange ratio, and blood lactate concentration during maximal exercise on treadmill in a large population.

Abbreviations: CPET = cardiopulmonary exercise test; FFM = fat-free mass; HR = heart rate; HRmax = maximal heart rate; MVV = maximal voluntary ventilation; RER = respiratory exchange ratio; V\textsuperscript{E}max = maximal minute ventilation; VO\textsubscript{2 max} = maximal oxygen uptake.
previously been reported, either for \( V_{\text{O2}} \) max alone, or in combination with other cardiorespiratory variables. However, the majority of these studies are old, and the inclusion criteria were often poorly described or set too low. Moreover, the end criteria for a true maximum effort may limit the clinician's ability to interpret CPET data. Therefore, the aim of this study was to determine the cardiorespiratory response during maximal exercise in a well-described representative national sample of 20- to 85-year-old men and women.

**Materials and Methods**

This study was part of a multicenter study involving nine regional test centers throughout Norway. The study was approved by the Regional Committee for Medical Ethics (REK Sur-Ost H; 2004/49) and the Norwegian Social Science Data Services, and the Norwegian Tax Department. All subjects signed written informed consent forms before participating. In 2008, 3,485 individuals underwent objective measurements of physical activity with the GT1M accelerometer (ActiGraph, LLC) and completed a questionnaire regarding exercise habits, income, level of education, and health status. The only inclusion criteria were age-related, and they were all randomly drawn from the areas surrounding each test center by the Norwegian population registry. From this sample of predominantly Caucasian individuals, 1,904 were randomly selected and invited to participate. Finally, a total of 904 men and women undertook the examination, and 759 successfully completed a maximal exercise test (Fig 1).

Before the CPET, information about each participant’s medical and smoking history was gathered. Participants with either two or more cardiovascular risk factors combined with an age of >50 years or with a BMI > 30 were excluded (n = 18). Height and body weight were measured to the nearest 0.5 cm and 0.1 kg, respectively, with participants wearing light clothes and no shoes. The percentage of fat for estimation of fat-free mass (FFM) was determined using three-site skinfold measurements by a skinfold caliper. The measurements were recorded at the chest, abdomen, and thigh for the men and at the triceps, suprailium, and thigh for the women. The following equation was used for percentage of fat: (405×body density) − 450. Specific equations were used for estimating the body density. Resting BP was manually measured in the sitting position (Big Ben; Rudolf Riester GmbH). Pulmonary function assessments were made according to the American Thoracic Society/European Respiratory Society guidelines.

CPET was performed on a treadmill using a stepwise modified Balke protocol until exhaustion. Gas exchange and ventilatory variables were measured continuously as the subjects breathed into a two-way breathing mask (2700 series; Hans Rudolph, Inc). Maximal BP was measured immediately after completion of the exercise test. The perceived exertion was rated by Borg scale.

A capillary blood sample was taken for lactate analysis about 60 s after termination of exercise (Lactate Pro, KDK Corporation or ABL 800, Radiometer Medical AS).

Three types of gas analyzers were used in the nine test centers: Oxycon Pro (Erich Jaeger GmbH; n = 2), Vmax SensorMedics (Carefusion Corporation; n = 6), and the Monox Modular \( V_{\text{O2}} \) system (AEI Technologies, Inc; n = 1). In addition to daily volume and gas calibrations, all analyzers were checked for measurement precision and accuracy with a standardized motorized mechanical lung (Motorized Syringe With Metabolic Calibration Kit, VacuMed) and/or a human calibrator. A correction factor was calculated for each gas analyzer to ensure reliable and comparable data between the test laboratories. The gas exchange variables were reported as 30-s averages. \( V_{\text{O2}} \) max was accepted if respiratory exchange ratio (BER) ≤ 1.10 or the Borg score was ≥ 17. The oxygen pulse was calculated by dividing \( V_{\text{O2}} \) max (in milliliters) by the maximal heart rate (HRmax). The breathing reserve (%) was calculated using the following equation: [(MVV − \( V_{\text{O2}} \) max)×MVV] × 100, where \( V_{\text{O2}} \) max is the maximal minute ventilation, and MVV (maximal voluntary ventilation) was estimated as FEV\(_1\) multiplied by 35 and/or a 12-lead ECG.

**Statistical Analysis**

Cross-sectional data are reported by age and sex, grouped into 10-year cohorts. Analysis of variance was used to evaluate differences in the cardiorespiratory variables between age groups tested by linear trends. Differences between the sexes were tested with Student’s t test. A linear regression analysis was performed according to age for \( V_{\text{O2}} \) max and HRmax. The correlation coefficient (r) and CI are reported. P values of ≤ .05 were considered statistically significant.

**Results**

This study examined 904 predominantly Caucasian subjects. Eighteen were excluded because of poor health, and 127 did not meet the criteria for maximal effort. Thus, 394 men and 365 women successfully achieved the \( V_{\text{O2}} \) max (84%). The mean baseline characteristics are shown according to 10-year age cohorts in Table 1 (women) and Table 2 (men). Tables 3 and 4 show the average cardiorespiratory variables measured at maximal exercise according to 10-year age cohorts for women and men, respectively. There was a significant difference between the sexes in \( V_{\text{O2}} \) max, \( V_{\text{E}} \) max, and maximal oxygen pulse, but no difference in HRmax, maximal respiratory exchange ratio, or Borg scale. Age clearly affected \( V_{\text{O2}} \) max, HRmax, maximal oxygen pulse, and \( V_{\text{E}} \) max (P < .001); had less influence on maximal respiratory exchange ratio, blood lactate concentration, and systolic BP; and had no effect on the breathing reserve, diastolic BP, or Borg scale.

The absolute value of \( V_{\text{O2}} \) max (L/min) in the women was, on average, 33% lower than that of the men (P < .001). Predictive equation was described by the following equation for men: \( V_{\text{O2}} \) max = 4.97 − 0.033 × year (r = 0.65; CI, 0.59-0.70) and for women: \( V_{\text{O2}} \) max = 3.31 − 0.022 × year (r = 0.64; CI, 0.58-0.70).
The \( \dot{V}O_2 \) max expressed relative to body mass (mL/kg/min) in the 20- to 29-year cohort was 48.6 (±9.58) for men and 40.3 (±7.14) for women, and declined with each 10-year in cohort by, on average, 4.2 mL/kg/min (9%) and 3.2 mL/kg/min (8%), respectively. The prediction equation for the men was: 
\[
\dot{V}O_2\text{ max} = 60.9 - 0.43 \times \text{year} \quad (r = 0.61; CI, 0.54-0.67)
\]
and for women: 
\[
\dot{V}O_2\text{ max} = 48.2 - 0.32 \times \text{year} \quad (r = 0.61; CI, 0.54-0.67).
\]

The \( \dot{V}O_2 \) max expressed relative to FFM (mL/kgFFM/min) was on average 29.1% and 46.1% higher \((P < .001)\) than \( \dot{V}O_2 \) max expressed relative to body mass for men and women, respectively.

The average HRmax was 194 beats/min (±7.84) in the 20- to 29-year age cohort, and declined with age in both sexes, by about 7.6 beats/min \((P < .001)\) per cohort (Fig 2). The HRmax showed the following age relationship for men:
\[
\text{HRmax} = 220 - 0.88 \times \text{year} \quad (r = 0.61; CI, 0.54-0.67)
\]
and for women:
\[
\text{HRmax} = 216.9 - 0.53 \times \text{year} \quad (r = 0.61; CI, 0.54-0.67).
\]

Table 1—Baseline Characteristics of Women by Age

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Age, y</th>
<th>20-29</th>
<th>30-39</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>70-85</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td></td>
<td>37</td>
<td>63</td>
<td>87</td>
<td>80</td>
<td>60</td>
<td>41</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td>25.6 (2.7)</td>
<td>35.8 (2.6)</td>
<td>45.2 (2.8)</td>
<td>54.9 (2.8)</td>
<td>64.5 (2.6)</td>
<td>76.0 (4.5)</td>
</tr>
<tr>
<td>Height, cm</td>
<td></td>
<td>169.2 (8.4)</td>
<td>167.6 (5.4)</td>
<td>167.3 (6.1)</td>
<td>166.3 (5.3)</td>
<td>164.8 (6.0)</td>
<td>161.1 (6.2)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td></td>
<td>66.5 (8.2)</td>
<td>68.9 (12.0)</td>
<td>72.4 (15.7)</td>
<td>71.9 (12.2)</td>
<td>68.1 (11.2)</td>
<td>66.2 (8.8)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td>23.3 (3.5)</td>
<td>24.5 (4.0)</td>
<td>25.8 (5.0)</td>
<td>25.7 (4.3)</td>
<td>25.5 (4.1)</td>
<td>25.6 (3.8)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td></td>
<td>81.2 (9.2)</td>
<td>81.9 (10.8)</td>
<td>84.4 (13.2)</td>
<td>86.8 (11.0)</td>
<td>86.9 (10.4)</td>
<td>87.6 (10.5)</td>
</tr>
<tr>
<td>Resting systolic BP, mm Hg</td>
<td></td>
<td>119.4 (9.8)</td>
<td>120.2 (11.3)</td>
<td>129.5 (15.6)</td>
<td>133.7 (13.9)</td>
<td>137.1 (18.6)</td>
<td>144.2 (18.5)</td>
</tr>
<tr>
<td>Resting diastolic BP, mm Hg</td>
<td></td>
<td>75.2 (7.2)</td>
<td>76.0 (8.2)</td>
<td>78.5 (9.3)</td>
<td>85.8 (8.8)</td>
<td>83.5 (10.2)</td>
<td>82.4 (9.5)</td>
</tr>
<tr>
<td>FVC, L</td>
<td></td>
<td>4.3 (0.7)</td>
<td>4.1 (0.6)</td>
<td>3.8 (0.7)</td>
<td>3.7 (0.6)</td>
<td>3.4 (0.5)</td>
<td>3.1 (0.5)</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td></td>
<td>3.5 (0.5)</td>
<td>3.2 (0.5)</td>
<td>3.0 (0.5)</td>
<td>2.8 (0.4)</td>
<td>2.5 (0.3)</td>
<td>2.2 (0.4)</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td></td>
<td>81.3 (6.5)</td>
<td>79.5 (6.1)</td>
<td>78.6 (6.0)</td>
<td>77.8 (6.1)</td>
<td>74.5 (6.7)</td>
<td>72.6 (6.0)</td>
</tr>
<tr>
<td>Activity, accelerometer counts/min</td>
<td></td>
<td>417.3 (164.5)</td>
<td>347.1 (100.6)</td>
<td>371.3 (116.0)</td>
<td>324.3 (88.4)</td>
<td>379.9 (111.8)</td>
<td>284.9 (129.3)</td>
</tr>
</tbody>
</table>

Educational level, No. (%)  

| Less than high school | 0 (0) | 1 (2) | 5 (6) | 8 (10) | 16 (27) | 6 (15) |
| University, < 4 y     | 9 (24) | 14 (22) | 25 (29) | 30 (38) | 10 (17) | 9 (20) |
| University, ≥ 4 y     | 11 (30) | 37 (59) | 22 (25) | 23 (29) | 17 (28) | 5 (12) |
| Smokers, No. (%)       | 5 (14) | 10 (16) | 17 (20) | 13 (16) | 6 (16) | 4 (10) |

Data are presented as mean (± SD) or No. (%).
Forty-four percent reached a plateau in oxygen uptake at the end of the protocol, defined as a leveling off in oxygen uptake despite an increase in ventilation at maximal work load. The average RER was 1.22 in the 20- to 49-year-old participants and decreased to 1.13 in the oldest age group (P = .002). There were no sex-related differences (P = .16). The average blood lactate concentration was 12.0 mmol/L in 20- to 49-year-old men and decreased linearly to 6.2 mmol/L in the oldest participants. The blood lactate concentration was significantly lower (by 10%) in women than in men across all age cohorts (P < .001), except ages of ≥60 years.

### Table 2—Baseline Characteristics of Men by Age

<table>
<thead>
<tr>
<th>Age, y</th>
<th>No. of subjects</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>BMI, kg/m^2</th>
<th>FVC, L</th>
<th>FEV₁/FVC, %</th>
<th>Resting systolic BP, mmHg</th>
<th>Resting diastolic BP, mmHg</th>
<th>BMI, kg/m^2</th>
<th>Weight, kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>38</td>
<td>182.4 (5.5)</td>
<td>81.5 (10.8)</td>
<td>24.5 (3.2)</td>
<td>6.0 (0.7)</td>
<td>79.5 (6.7)</td>
<td>159.8 (18.9)</td>
<td>72.3 (17.1)</td>
<td>81.5 (10.8)</td>
<td>24.5 (3.2)</td>
</tr>
<tr>
<td>30-39</td>
<td>74</td>
<td>181.2 (5.8)</td>
<td>84.4 (12.6)</td>
<td>25.7 (3.8)</td>
<td>6.5 (0.7)</td>
<td>79.4 (5.2)</td>
<td>169.6 (18.6)</td>
<td>75.5 (11.7)</td>
<td>84.4 (12.6)</td>
<td>25.7 (3.8)</td>
</tr>
<tr>
<td>40-49</td>
<td>91</td>
<td>178.9 (6.8)</td>
<td>84.8 (12.8)</td>
<td>26.4 (3.4)</td>
<td>6.8 (0.7)</td>
<td>77.9 (5.8)</td>
<td>177.2 (23.0)</td>
<td>76.2 (22.2)</td>
<td>84.8 (12.8)</td>
<td>26.4 (3.4)</td>
</tr>
<tr>
<td>50-59</td>
<td>98</td>
<td>179.2 (6.6)</td>
<td>86.2 (10.1)</td>
<td>26.8 (2.7)</td>
<td>7.0 (0.7)</td>
<td>75.8 (6.5)</td>
<td>182.4 (24.7)</td>
<td>81.2 (14.8)</td>
<td>86.2 (10.1)</td>
<td>26.8 (2.7)</td>
</tr>
<tr>
<td>60-69</td>
<td>83</td>
<td>178.1 (6.5)</td>
<td>85.5 (13.0)</td>
<td>26.9 (3.5)</td>
<td>7.2 (0.7)</td>
<td>73.7 (7.3)</td>
<td>190.2 (24.0)</td>
<td>80.1 (16.2)</td>
<td>85.5 (13.0)</td>
<td>26.9 (3.5)</td>
</tr>
<tr>
<td>70-85</td>
<td>24</td>
<td>176.3 (8.3)</td>
<td>82.5 (11.0)</td>
<td>26.5 (2.7)</td>
<td>7.4 (0.7)</td>
<td>73.1 (6.9)</td>
<td>192.7 (27.5)</td>
<td>81.0 (20.1)</td>
<td>82.5 (11.0)</td>
<td>26.5 (2.7)</td>
</tr>
</tbody>
</table>

Data are presented as mean (± SD) or No. (%).

### Table 3—Physiologic Responses at Maximal Exercise for Women

<table>
<thead>
<tr>
<th>Age, y</th>
<th>No. of subjects</th>
<th>VO₂max L/min</th>
<th>VO₂max mL/kg/min</th>
<th>VO₂max mL/kg/FM/min</th>
<th>VO₂max leveling-off, %</th>
<th>VO₂max oxygen-pulse, mL/beat</th>
<th>Oxygen pulse, mL/beat</th>
<th>RER</th>
<th>CO₂ output, mL/min</th>
<th>CO₂ output, mL/kg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>37</td>
<td>2.66 (0.47)</td>
<td>40.3 (7.1)</td>
<td>55.9 (9.1)</td>
<td>38</td>
<td>1.40 (2.6)</td>
<td>13.6 (2.2)</td>
<td>1.22</td>
<td>1.12 (0.10)</td>
<td>11.7 (0.8)</td>
</tr>
<tr>
<td>30-39</td>
<td>63</td>
<td>2.54 (0.41)</td>
<td>37.6 (7.5)</td>
<td>53.5 (8.1)</td>
<td>49</td>
<td>1.36 (2.2)</td>
<td>12.9 (2.4)</td>
<td>1.22</td>
<td>1.12 (0.10)</td>
<td>11.7 (0.8)</td>
</tr>
<tr>
<td>40-49</td>
<td>96</td>
<td>2.33 (0.42)</td>
<td>33.0 (6.4)</td>
<td>49.0 (6.9)</td>
<td>37</td>
<td>1.29 (2.4)</td>
<td>12.3 (2.3)</td>
<td>1.22</td>
<td>1.12 (0.10)</td>
<td>11.7 (0.8)</td>
</tr>
<tr>
<td>50-59</td>
<td>79</td>
<td>2.14 (0.41)</td>
<td>30.4 (5.1)</td>
<td>46.2 (7.6)</td>
<td>46</td>
<td>1.20 (2.0)</td>
<td>11.6 (2.3)</td>
<td>1.22</td>
<td>1.12 (0.10)</td>
<td>11.7 (0.8)</td>
</tr>
<tr>
<td>60-69</td>
<td>79</td>
<td>1.94 (0.39)</td>
<td>28.7 (6.6)</td>
<td>42.4 (8.8)</td>
<td>44</td>
<td>1.18 (0.18)</td>
<td>11.5 (2.3)</td>
<td>1.22</td>
<td>1.12 (0.10)</td>
<td>11.7 (0.8)</td>
</tr>
<tr>
<td>70-85</td>
<td>59</td>
<td>1.54 (0.27)</td>
<td>23.5 (4.1)</td>
<td>34.7 (5.8)</td>
<td>39</td>
<td>1.13 (0.12)</td>
<td>9.8 (1.8)</td>
<td>1.22</td>
<td>1.12 (0.10)</td>
<td>11.7 (0.8)</td>
</tr>
</tbody>
</table>

Data are presented as mean (± SD). FFM = fat-free mass; RER = respiratory exchange ratio; VO₂ = CO₂ output; VO₂max = maximal minute ventilation; VO₂uptake = oxygen uptake; VO₂max = maximal oxygen uptake.
**Discussion**

This national cohort study presents reference values for the interpretation of CPET derived from a randomly selected sample of 759 apparently healthy men and women aged 20 to 85 years. We have demonstrated that the VO2 max relative to body mass is about 25% higher in men than in women, the decline in VO2 max with age in both sexes, even though the age-related subjective Borg scale was unchanged. The participation rate from the original invited population of 3,485 after telephone contact was 66%. Given that all the participants had to come to the examination during the day and several had to travel quite long distances, the participation rate seems high. Nevertheless, a comprehensive nonresponse analysis was undertaken, and showed that there was a clear selection bias insofar as the respondents had a higher educational status than the nonrespondents. Therefore, the participants in the present study may have had better health and consequently greater cardiorespiratory fitness than the nonrespondents.

The end criterion chosen for an acceptable VO2 max was an RER ≥ 1.10 or a Borg score of ≥ 17. Some studies have not reported the end criteria for acceptable tests, but have chosen a low criterion for RER (≤ 1.0), or based the participants' maximal limit at an imprecise estimation of HR. These factors may increase the likelihood of underestimating or overestimating the variables. Compared with other studies, these end criteria are strict. This was also confirmed by a higher average HRmax in each age group compared with other studies. Although HRmax is not a variable that predicts maximum effort well, it provides a good picture of the degree of fatigue in larger groups.

Blood lactate was measured at the end of the test to quantify the anaerobic energy consumption. The results showed high values in the youngest subjects, dropping by 50% in the oldest subjects, demonstrating their smaller capacity for blood lactate production.

**Cardiorespiratory Fitness**

To our knowledge, only two studies have investigated the CPET response on a treadmill in a large healthy population. The retrospective study of Nelson et al used the same exercise protocol and end criteria for a maximal test as used in the current study. The VO2 max relative to body weight was 5% lower, on average, than in the comparable age groups in our study, which can be largely explained by the 6% higher body weight of the Canadian men. The study by Inbar et al of Israeli men also found a lower VO2 max. The average HRmax of the Israeli men was lower at comparable ages and may indicate that the CPET was terminated at a lower effort, leading to a lower VO2 max. This emphasizes the importance of pushing the subjects to their maximum to ensure valid measurements.

A new set of VO2 max values has recently been published for an impressively large sample that included both men and women. The HUNT Fitness Study investigated 4,631 healthy 20- to 90-year-old men and women.
women on a treadmill. The \( V_{O2} \text{max} \) was, on average, 9% higher in the HUNT study than in the present study for all cohorts and both sexes, even though we used a stricter end criterion for \( V_{O2} \text{max} \) and excluded all subjects who did not reach the established criterion, in contrast to the HUNT study. However, due to the lack of HRmax and blood lactate values, it is difficult to say whether the participants reached the same level of exhaustion as those in the HUNT study. Nevertheless, one explanation for the high level of \( V_{O2} \text{max} \) in the HUNT study may be the type of gas exchange analyzer used (portable MetaMax). It has previously been documented in a validation study that the portable MetaMax system measures 8% higher than the gold standard Douglas bag system.\(^{27}\) This may be the main explanation for the higher \( V_{O2} \text{max} \) values reported.

Regarding obesity, which is rapidly increasing, obese individuals have been shown to have a high absolute \( V_{O2} \text{max} \) and a low \( V_{O2} \text{max} \) relative to body weight with a lower performance, compared with lean individuals.\(^{28,29}\) When comparing the physiologic ability for the tissue to maximally consume oxygen, \( V_{O2} \text{max} \) may, therefore, better be expressed relative to FFM in obese individuals.\(^{29}\)

In the current study, HR measured at maximal exercise was somewhat higher than those in other large population studies.\(^{3,6,11-14}\) Not surprisingly, the variability was large, increasing in each age cohort, and differed significantly in all age cohorts from the common predictive equation \( HR_{\text{max}} = 220 - \text{age}. \) The predicted value for \( HR_{\text{max}} \) based on this formula may underestimate the average measured \( HR_{\text{max}} \). Furthermore, the \( HR_{\text{max}} \) SD was as high as \( \pm 14.0 \) beats/min in the oldest age cohort (70-85 years). These findings correspond to those of previous studies\(^{7,12}\) and may highlight the inaccuracy of the formula. Hence, a physician who stops the exercise test based on the predicted \( HR_{\text{max}} \) is likely to underestimate the maximal effort. This may lead to false negative findings, and a significant coronary artery disease might be missed.

The relationship between \( HR_{\text{max}} \) and \( V_{O2} \text{max} \), termed the “oxygen pulse,” reflects the maximal amount of oxygen extracted per heart beat and yields information on the maximal cardiac stroke volume. Therefore, a low oxygen pulse may reflect cardiac limitations if the patient does not desaturate.\(^{31}\) Our data for men are consistent with the recent report of Nelson et al.\(^{13}\) who used the same ergometer and end criteria as that used in this study.

During CPET, the peak minute ventilation is important for the determination of the breathing reserve in order to interpret pulmonary limitation.\(^{20}\) The average breathing reserve was 23% for men and 30% for women, which are consistent with previous findings.\(^{11}\) This confirms that untrained subjects do not ordinarily have ventilatory limitations on their ability to perform work.\(^{32}\) Unfortunately, the MVV was not measured directly, but estimated as \( FEV_1 \times 35 \) and 40, which may underestimate the breathing reserve.\(^{21}\)
Strengths and Limitations

The main strengths of the present study were its large and well-described sample of men and women, their random inclusion from rural and nonrural populations, and the wide age range. Furthermore, the end criteria used for VO\textsubscript{2max} were rather strict compared with those of other studies,\textsuperscript{3,6,10-12,14} and blood lactate concentration was measured at the end of the test to quantify the anaerobic energy consumption.

The limitation of the study was the use of nine different test laboratories, including three different gas analyzer models, which may have increased the possibility of different test methods and measurement accuracies across the test laboratories. However, some initiatives were taken to minimize these differences. First, all the technicians were rigorously trained in all test procedures and they were experienced with maximal exercise testing. Second, all the gas analyzers were calibrated to an artificial lung.

Conclusions

In summary, this is the first investigation to evaluate a large and well-described population including different maximal cardiorespiratory fitness variables for both men and women on a treadmill across all ages from 20 to 85 years. The statistical analysis focused on the relationship between age and the different physiologic variables used in a typical clinical setting. These results can be used as reference variables during CPET on a treadmill.

Acknowledgments

Author contributions: Ms. Edvardsen is guarantor of the study and takes responsibility for the accuracy of the data. Ms. Edvardsen contributed by actively planning the study; controlling the equipment and quality of the test procedures; collecting, analyzing, and interpreting the data; and drafting the manuscript.

Dr. Hansen contributed to the conception and design of the study; coordinated the data collection, analyzed the data, and reviewed the manuscript critically.

Dr. Holme contributed to the conception and design of the study; was particularly active in the statistical guidance; and reviewed the manuscript critically.

Dr. Dyrdal contributed by actively planning the study, collecting data, and reviewed the manuscript critically.

Dr. Andersen contributed as project manager of the study; actively participating in the design and conception of the study and the article; discussing the interpretation of the data, and reviewing the manuscript critically.

Financial/nonfinancial disclosures: The authors have reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsor had no role in the design of the study, the collection, analysis, and interpretation of the data, or in the preparation of the manuscript.

Other contributions: We thank all the test personnel for their work during the data collection at the nine institutions involved in the study: Finnmark University College, Hedmark University College, NTNU Samfunnsforsking AS, Sogn og Fjordane University College, University of Agder, Universitet i Nordland, University of Stavanger, Telemark University College, and Oslo University Hospital, Ullevål.

References

Paper II
End Criteria for Reaching Maximal Oxygen Uptake Must Be Strict and Adjusted to Sex and Age: A Cross-Sectional Study

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1 Norwegian School of Sport Sciences, Department of Sports Medicine, Oslo, Norway, 2 Oslo University Hospital, Ullevål, Department of Pulmonary Medicine, Oslo, Norway

Abstract

Objective: To describe different end criteria for reaching maximal oxygen uptake (VO2max) during a continuous graded exercise test on the treadmill, and to explore the manner by which different end criteria have an impact on the magnitude of the VO2max result.

Methods: A sample of 861 individuals (390 women) aged 20–85 years performed an exercise test on a treadmill until exhaustion. Gas exchange, heart rate, blood lactate concentration and Borg Scale rating were measured, and the impact of different end criteria on VO2max was studied.

Results: Eight hundred and four healthy participants (93%) fulfilled the exercise test until voluntary exhaustion. There were no sex-related differences in HRmax, RER, or Borg Scale rating, whereas blood lactate concentration was 18% lower in women (P = 0.001). Forty-two percent of the participants achieved a plateau in VO2; these individuals had 5% higher ventilation (P = 0.033), 4% higher RER (P < 0.001), and 5% higher blood lactate concentration (P = 0.047) compared with participants who did not reach a VO2 plateau. When using RER ≥1.15 or blood lactate concentration ≥8.0 mmolL−1, VO2max was 4% (P = 0.012) and 10% greater (P < 0.001), respectively. A blood lactate concentration ≥8.0 mmolL−1 excluded 63% of the participants in the 50–85-year-old cohort.

Conclusions: A range of typical end criteria are presented in a random sample of subjects aged 20–85 years. The choice of end criteria will have an impact on the number of the participants as well as the VO2max outcome. Suggestions for new recommendations are given.

Introduction

The measurement of maximal oxygen uptake (VO2max) has been available for more than half a century and provides useful information about an individual's maximal cardiorespiratory fitness and level of physical performance. During the exercise test, the technicians' skills and the subjects' motivation and effort are important requirements to ensure valid and reliable results when comparing groups in large epidemiological surveys, as well as for the accurate interpretation of a maximal test for both athletes and patients. The classical plateau described by Taylor and coworkers is recognized as the gold standard to determine a true VO2max [1]. However, this criterion is not straightforward to use in practical settings [2]. Therefore, a large variety of other end criteria have been used, such as an elevated respiratory exchange ratio (RER) ≥1.0 [3–5], 1.10 [6,7], or 1.15 [8,9], the achievement of a certain percentage of the age-adjusted estimate of HRmax [7,10,11], high postexercise blood lactate levels (≥8 mmolL−1) [8,12], the subject's rating of perceived exertion (Borg Scale rating or Visual Analog Scale) [13], or a combination of the above-mentioned variables [14]. Thus, there is currently no consensus regarding the assessment of maximal effort during a continuous graded exercise test on the treadmill – especially among women and the elderly – and the knowledge about how different end criteria variables are affected by gender and aging is scarce. Furthermore, the original recommendations are often based on older studies that used measurement equipment and test protocols that are different from those used today [1,15], and the number of participants was low [7,9,16,17] or consisted of athletes or children and adolescents [7,15,18–20]. Therefore, the purpose of this study was to describe the different end criteria that are used often for reaching VO2max during a maximal progressive graded exercise test on the treadmill in a healthy sample of 20–85-year-old men and women, and to explore if the choice of end criteria has an impact on the VO2max value.
Table 1. Baseline characteristics of the participants by 15-year age cohort for female and male (SD).

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–34</td>
<td>40</td>
<td>33</td>
</tr>
<tr>
<td>35–49</td>
<td>39</td>
<td>46</td>
</tr>
<tr>
<td>50–64</td>
<td>46</td>
<td>36</td>
</tr>
<tr>
<td>65–85</td>
<td>37</td>
<td>31</td>
</tr>
</tbody>
</table>

Table 2. End criteria variables during maximal exercise by 15-year age cohort for female and male (SD).

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–34</td>
<td>3.12</td>
<td>3.01</td>
</tr>
<tr>
<td>35–49</td>
<td>3.06</td>
<td>3.04</td>
</tr>
<tr>
<td>50–64</td>
<td>3.02</td>
<td>2.98</td>
</tr>
<tr>
<td>65–85</td>
<td>3.05</td>
<td>2.99</td>
</tr>
</tbody>
</table>

Exercise Test

Height and body weight were measured to the nearest 0.5 cm and 0.1 kg, respectively, with participant’s wearing no shoes and light clothes. The exercise test was performed during daytime by walking and running on a treadmill using a modified Balke protocol [22]. Four minutes of warm-up were performed with the treadmill speed set at 4.8 km·h⁻¹ and inclination set at 4%. For participants who were older than 55 years or were obese, the speed was set at 3.8 km·h⁻¹. The inclination was then increased each 60 s by 2%, up to a 20% inclination. If the participant was still able to continue, the speed was further increased by 0.5 km·h⁻¹ until exhaustion. Gas exchange and ventilatory variables were measured continuously as the subjects breathed into a Hans Rudolph two-way breathing mask 2700 series, Hans Rudolph Inc., Shawnee, KS, USA. During the last part of the test, the subject’s effort was largely encouraged by the technician until voluntary termination. The rating of perceived exertion was obtained using the Borg Scale [23]. A capillary blood sample was taken 60 s after termination of the exercise test and analyzed for blood lactate concentration using hemolyzed blood (Lactate Pro; KDK Corporation, Kyoto, Japan; or ABL 100; Radiometer Medical, Copenhagen, Denmark).

The gas analyzers used were daily volume- and gas calibrated corrected for barometric pressure, temperature and humidity. A detailed descriptions regarding measurement accuracy between gas analyzers is given elsewhere [14]. The gas-exchange variables were reported as 30 s averages. HR was recorded each minute using a Polar Sports Watch (Kempele, Finland) or 12-lead ECG. The highest VO₂peak during 30 s stage was used, and the highest RER measured before or corresponding to the last 30 s stage was reported. A plateau in VO₂ was defined as any two 30-s VO₂ values in which the second was not higher than the first, provided increase in ventilation at maximal effort. Participants who did not exhibit an increase in ventilation despite achievement of a plateau only inclusion criterion was age-related, and 1,930 of the subjects were randomly invited to participate in a sub study during 2009–2010, including a cardiopulmonary exercise test (CPET) on a treadmill [14]. Finally, a total of 904 men and women met at the laboratory and 804 completed CPET to exhaustion.

Materials and Methods

Ethics Statement

The study was approved by the Regional Committee for Medical Ethics (REK South-Eastern Norway B, S-08046b), the Norwegian Social Science Data Services AS, and the Norwegian Medical Ethics (REK South-Eastern Norway B, S-08046b), the Norwegian Tax Department. All individuals signed written informed consent forms before participating.

Study Design

This study was a cross-sectional multicenter study involving nine test centers from all regions of Norway. The participants were healthy men and women aged 20–85 years who participated in the population-based KAN study carried out in 2008/2009 [21]. The

<table>
<thead>
<tr>
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Materials and Methods

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Figure 1. Maximal oxygen uptake (VO2max) using different end criteria (dark grey) compared to volitional fatigue (all) (mean ± SD). The light grey bars show VO2max in those subjects who did not fulfill the end criterion. The % of participants who fulfilled the criterion is reported on each bar.

doi:10.1371/journal.pone.0085276.g001

Figure 2. Oxygen uptake (mL·kg⁻¹·min⁻¹) and minute ventilation (L·min⁻¹) from table 3 plotted against time (min). The arrows' pointing downward indicates a drop in ventilation followed by a levelling off in VO2, marked by a circle. The right pointing arrow indicates the expecting increase in VO2.

doi:10.1371/journal.pone.0085276.g002
were not accepted. This to ensure that the subject had reached the respiratory compensation point caused by metabolic acidosis.

The different end criteria used to study the impact on VO₂max were VO₂ leveling off, RER max $\geq 1.0, 1.10, \text{ and } 1.15, \text{ blood lactate concentration } \geq 6.0 \text{ and } 8.0 \text{ mmol } N \text{L}^{-1}, \text{ Borg Scale } 6-20 \text{ rating, and HR max } \leq 95\% \text{ of the age-predicted HR max (220 - age)} \text{ compared with symptom-limiting termination of the test.}

Statistical Analysis

Demographic data were presented as mean values ± standard derivation (SD), and cross-sectional data were reported according to age and sex and grouped into 15-year cohorts. Analysis of variance (ANOVA) was used to evaluate differences in the end-criteria variables between age groups. A test of trend was performed with x values equal to the average within each age category. The effects of the end criteria on VO₂max were tested using Student’s t test. Correlations between the commonly accepted end criteria were assessed using Pearson’s correlation coefficient (r). Statistical tests were conducted using SPSS version 18.0 (SPSS, Chicago, Illinois, USA). P values of ≤0.05 were considered statistically significant.

The new recommendations for maximal effort are based on mean values for postexercise blood lactate concentration and RER – 1 SD, which included 84% of the participants. To simplify, the blood lactate recommendations are reported to the nearest 0.5 mmol $N\text{L}^{-1}$.

Criteria for Maximum Effort during VO₂max

### Results

This study examined 861 subjects during exercise testing on a treadmill. Thirty subjects ended the study prematurely or were excluded because of medical considerations, and 27 participants were not able to perform the test to voluntary exhaustion. The participants’ characteristics according to 15-year cohorts are shown in Table 1.

### Maximal Exercise

The main subjective reason for stopping exercise was dyspnea in women (54%) and muscular fatigue in men (38%). General fatigue was reported in 28% of the subjects. There was no age-related influence on the reason for ending the test. The maximum end criteria variables are given in Table 2.

#### Table 3. Raw data from baseline to limit of tolerance during a maximal progressive graded exercise test.

<table>
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<th>Time (min)</th>
<th>Speed (km-h⁻¹)</th>
<th>Elevation (%)</th>
<th>VO₂ (mL-min⁻¹)</th>
<th>VO₂ (mL·kg⁻¹·min⁻¹)</th>
<th>VE (L·min⁻¹)</th>
<th>RER (VO₂/VO₂)</th>
<th>HR (s·min⁻¹)</th>
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</table>

HR = Heart rate; RER = Respiratory Exchange Ratio; RPE = Rating of Perceived Exertion; VE = Ventilation; VO₂ = Oxygen uptake.

The bold numbers followed by an elevated number indicate a plateau in oxygen uptake (VO₂) during the test. Note that at least six plateau occurred after the 4 minute during the test, two after RER ≥1.15.

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End Criteria and Impact on Oxygen Uptake

The dark grey bars in Figure 1 shows VO2max using different end criteria compared to voluntary exhaustion. When using RER ≥1.15, the VO2max was 4% greater (P=0.012) compared to subjects who did not reach the same criterion. Furthermore, RER ≥1.15 excluded 281 subjects (35%) from the population. After age adjustment, there was no change in VO2max between the different method (P=0.923). Correspondingly, when using only a blood lactate concentration ≥6.0 mmol L−1, the VO2max was 4% (P=0.004) and 10% (P=0.001) greater. The difference was highest after 50 years of age (P=0.001).

The difference between the dark grey and light grey bars in Figure 1 shows the difference in VO2max between the subjects who fulfilled and those who did not fulfill the different end criteria. The largest difference in VO2max was observed in VO2max, which fulfilled and those who did not fulfill the blood lactate concentration criterion and RER ≥1.0.

Discussion

The purpose of this study was to describe different end criteria for reaching VO2max during a progressive maximal treadmill test in a healthy sample of 20-45-year-old men and women, and to explore if the choice of end criteria had an impact on the VO2max value. The major findings were that the postexercise blood lactate concentration and RER decreased with age, despite the fact that the subjective ratings of exertion related to age remained unchanged. Furthermore, choosing a lactate concentration ≥6.0 and/or RER ≥1.15 yielded a higher VO2max, but excluded a significant number of participants from the analysis.

End Criteria Variables for Maximal Oxygen Uptake

The classical criterion for VO2max is achievement of a plateau in VO2 despite an increase in work rate. A RER above a certain level, a high level of blood lactic acid, and age-adjusted estimates of HRmax are also used, especially in subjects who failed to achieve a plateau [8]. The higher HRmax achieved in each age group compared with other similar studies [6,19,24] allows us to state the high validity of our data. It also reflects differences between subjects in the degree of motivating the subjects to exhaustion, which underlines the importance of using equal end-criteria in large epidemiological studies. There was, however, a substantial range of maximal values for each of the reported end variables according to age and sex blood lactate concentration, 1.2-18 mmol L−1, RER, 0.85-1.57, HRmax, 75-137% predicted based on 220 age, which complicates the interpretation of the results and, thus, may be of major concern when choosing optimal criteria during exercise testing.

VO2 Plateau. A plateau in VO2 was found in 42% of the subjects and was defined as a VO2 leveling off, despite a rise in ventilation, which is in line with findings from other investigations [19,20]. Our definition differs from the classical definition of a plateau described by Taylor and co-workers [1]. Taylor performed several systematic “steady state” tests over 3-5 days using Douglas bags, and found that the increase in VO2 during the treadmill protocol from day to day was approximately 4.2±1.1 mL kg−1 min−1. Based on this observation, those authors claimed that an increase of less than 2 SD of the expected rise in VO2 satisfies a
plateau, representing less than 2.1 mL kg\(^{-1}\) min\(^{-1}\) to the next level, or less than 150 mL min\(^{-1}\) if the participant’s body mass was 72 kg [1].

Despite that the Taylor’s method is considered the gold standard for defining VO\(_{2}\)max, there are several reasons why we did not chose this method during the continuous graded exercise protocol. First, our protocol included a much smaller increase in workload. A smaller increase in workload may lead to measurements that exhibit more fluctuation regarding VO\(_2\) between each sampling. As outlined in Table 3, a continuous graded protocol may lead to the achievement of several VO\(_2\) plateaus during the test, also above RER = 1.15, which may preclude the recording of a valid VO\(_{2}\)max. Second, the body mass of many of the participants in the current study differed substantially from 72 kg, which hampers the comparison between studies. Third, the use of minute ventilation instead of workload was chosen to ensure that subjects had reached their respiratory compensation point at the end of the test, also illustrated in Figure 2. The respiratory compensation point reflects the final phase of exercise, at which hyperventilation occurs in order to decrease the arterial p\(_{\text{O}_2}\) resulting from metabolic acidosis [25]. In addition, the measurement of ventilation is online at any time, following simultaneously the subject’s breathing pattern, while expiratory gases will be delayed to a greater or lesser extent depending on the size of the ventilation. Thus, if ventilation increases and oxygen uptake is constant during increased workload, it is reasonable to assume that the gas exchange has reached its maximum uptake (Figure 2).

Based on the reasons mentioned above, and taking into account the fast electronic, real time gas analyzers that are available currently, the cutoff value proposed by Taylor seems to be too liberal, and should therefore not be used during continuous graded protocols, especially in elderly patients or in unfit subjects, for whom the increase in workload is low.

Reaching a plateau in VO\(_2\) during a progressive exercise test places great demands on the anaerobic energy consumption. This may be a challenge, especially for untrained or elderly subjects, who are not familiar with the unpleasant feelings associated with strenuous activities [26]. There was, however, no relationship between fitness level and age regarding achievement of a plateau in the current study, with the exception of the oldest age cohort of men (data not shown). Nevertheless, only 65% of those who reached a plateau fulfilled the blood lactate concentration criterion of $8.0 \text{ mmol} L^{-1}$ if the participant’s body mass was 72 kg.

### Respiratory Exchange Ratio

In cases of failure to achieve a plateau in VO\(_2\), RER is the most-used secondary criterion for attaining VO\(_{2}\)max [0]. The rise in RER during heavy exercise is caused by an imbalance between the production and the elimination of lactic acid, because of the increase in the buffering of lactate [16]. In addition, as CO\(_2\) is generated from muscle work, the rise in ventilation increases the RER [8]. Therefore, it seems logical that if the blood lactate concentration is high, the RER would be high. This is in line with the results of the present study, which showed that 84% of the individuals with a blood lactate concentration $\geq 8.0 \text{ mmol} L^{-1}$ had RER $\geq 1.15$.

Despite the fact that RER $\geq 1.15$ is the originally recommended secondary end criterion [9], lower RER\(_{\text{max}}\) cutoff values have been used, such as $\geq 1.10$ [6], $\geq 1.05$ [5], or $\geq 1.0$ [4]. Only 65% of the subjects enrolled in the present study reached RER $\geq 1.15$. Even though the association with age was weak ($r = -0.304$), there was a reduction in RER in each age cohort after 50 years of age, despite the fact that the subjective ratings of perceived exertion was unchanged. The decrease in RER in the elderly is based on a shift from type II to type I fibers and corresponding metabolic shift towards an oxidative (lipid) preferential phenotype. Thus, RER should be adjusted for age when used as a criterion for establishing of VO\(_{2}\)max.

### Blood Lactate Accumulation

Blood lactate is a good indicator of a high effort, as high blood lactate levels are associated with fast-twitch fiber recruitment [27] and a progressive or sharp decrease in intracellular p\(_{\text{O}_2}\) [28]. Here, the postexercise blood lactate concentration decreased with increasing age, especially after 50 years of age. Choosing the well-known 8 mmol L\(^{-1}\) end criterion, which is based originally on findings from 14-16-year-old boys and girls [15], led to the exclusion of 63% of the participants in the 50-85-year-old cohort. Sidney and Shephard [29] also found a lower incidence of reaching a high level of blood lactate concentration in the elderly, even though a plateau in VO\(_2\) was achieved in these individuals. Lower blood lactate accumulation in the elderly may be explained by dyspnea, loss of type II fibers followed by muscular weakness, and lower capacity for anaerobic glycolysis [25]. Thus, this is an expected finding, and therefore the potential for lactate accumulation is reduced by age. Even though the RER value and the incidence of a plateau were similar between the sexes, women had a significantly lower blood lactate concentration compared with men. This is in accordance with previous studies performed using both trained and untrained subjects [30,31] and suggests that men have a greater capacity than women to generate ATP via anaerobic glycolysis. In addition, women have a smaller ratio of muscle mass to total blood volume [29] and achieve lower workloads on the treadmill compared with men. A higher workload suggests greater energy turnover and more glycolytic flux, which may lead to greater lactate levels [32]. Such a difference between sexes should be taken into account when evaluating maximal effort using blood lactate as a criterion.

The assessment of postexercise blood lactate concentration is a non-manipulative variable, in contrast to RER (breathing pattern) or HR (psychological factors). This assessment is easy to perform and has a high measurement accuracy; thus, it represents a more objective physiological reflection of the amount of high-intensity exercise compared with VO\(_2\) leveling off, RER, or the percentage of the HR predicted. Despite the essential nature of this variable, we have only been able to find one epidemiological study reporting cardiorespiratory fitness variables in a population with measured blood lactate levels [33]. Based on the reasons mentioned above, we recommend that this variable should be used more frequently.

### Maximal Heart Rate

HR\(_{\text{max}}\) differed significantly in all age cohorts from the commonly used formula of 220-age. Furthermore, the standard deviation was high ($\pm 15.0$) in the 65-85-year-old cohort, making it very difficult to justify the use of this variable as a standard (because of its wide range). These findings are in line with those of previous studies [5,24], and the use of a certain percentage of the age-adjusted HR\(_{\text{max}}\) has been questioned [9]. The American College of Sports Medicine stated over 20 years ago that age-predicted HR\(_{\text{max}}\) should not be used as an absolute criterion for maximal effort, which is supported by our data.

### Rating of Perceived Exertion

The Borg Scale is widely used to measure exercise intensity, and there is a relationship between rating of perceived exertion and physiological measures such as HR and blood lactate concentration [34]. The Borg Scale has, however, produced inconsistencies regarding the strength of the relationships; in addition, its validity has been shown to be lower than was previously thought [35]. This is in agreement with the results of the current study, especially those of elderly men and women who scored high on the Borg Scale despite lower postexercise blood lactate concentration and RER.
Choice of End Criteria and Impact on the VO_{2max} Value

Reaching objective variables of maximal effort has been shown to be difficult for athletes [19,36], elderly people [13,29], obese individuals [26], sedentary people, and patients [37], and depends on the measurement method used, sampling interval [38], and type and duration of the test protocol [29]. Furthermore, the standards used for each of the maximum criteria exhibited great variability. Some of these may be too low [5] or totally absent [39], which may increase the likelihood of underestimating the VO_{2max} variable; or the opposite, too high, leading to the rejection of subjects who would actually achieve a valid VO_{2max} thereby giving an overestimation of the VO_{2max}. The choice of different end criteria for maximal effort in the present 20–85-year-old population had an impact on the number of participants included in each age cohort, sex, or the results, whereas a blood lactate concentration ≥2.0 and ≥2.0 mmolL⁻¹ and an RER ≥1.15 had the greatest impact on the VO_{2max} result.

Poole and co-workers [17] compared the VO_{2max} results obtained based on leveling-off criteria, which they defined as a true VO_{2max}, with the RER, blood lactate concentration, and age-predicted ḢV̇O_{2max} in eight young healthy men performing a cycle ramp protocol until exhaustion. They found that terminating the exercise test immediately after reaching the RER criteria of 1.10 or 1.15 led to an underestimation of the VO_{2max} of as much as 27% and 16%, respectively, compared with the results obtained based on leveling off. Furthermore, those authors found that the blood lactate concentration criterion was unusable because of the achievement of several plateaus during a continuous graded exercise test, rendering the interpretation of each measure meaningless. Stopping the exercise test based on the measurement and not because of exhaustion or voluntary determination is thus not meaningful.

New Recommendations

We have presented new recommendations for postexercise blood lactate concentrations and RER values (Table 4). These recommendations are based on the age and sex differences derived from the present results, as discussed previously, where both criteria must be fulfilled.

In our opinion, the use of VO_{2} leveling off is not recommended because of the achievement of several plateaus during a continuous graded exercise protocol, which is also supported by Noakes [41]. Therefore, it is easy to misinterpret these results during the test (Table 3, Figure 2). We chose the average value of blood lactate concentration and RER from each sex and age cohort minus one SD. This was chosen because the SD reflects the dispersion in each age cohort. However, using all accepted tests above one negative SD will reject 16% of the participants in each age group. As the concept of maximal oxygen uptake involves maximal aerobic energy metabolism, we have experienced that many will struggle to push enough to reach the needed level of exhaustion.

Strengths and Limitations

The main strengths of the current study were its large sample of both fit and unfit men and women, the random inclusion of participants from rural and nonrural populations, and the wide age range of the participants.

One of the limitations of the study was the use of nine different test laboratories, including a large number of technicians, which may have increased the possibility of different levels of encouragement regarding maximal effort, in addition to the possibility of achieving different measurement accuracies across laboratories. However, some initiatives were taken to minimize these issues. First, all the technicians were rigorously trained in all test procedures and were experienced with maximal-exercise testing. Second, all gas analyzers were checked for measurement precision and accuracy using a standardized motorized mechanical lung (Motorized Syringe with Metabolic Calibration Kit; VacuMed, Ventura, CA, USA). Third, use of different technicians reflects the “real life” situation, thus being more representative.

Conclusion

A range of typical end criteria were presented in a random sample of healthy men and women aged 20–85 years. The choice of end criteria during exercise testing had an impact on sex and the number of participants, and some impact on the outcome of the test. Based on these results, new recommendations are given according to age and sex for individuals using a continuous graded exercise test on a treadmill. Studies with other populations should be applied to confirm our results.

Acknowledgments

The authors thank all the brilliant test personnel at the nine institutions involved in the study for their work during the data collection. Sigurd Bøhlo (Funnark University College), Jon Egl Jakobsen (Hedmark University College), Nils Petter Aspvik and Oddbjørn Flosen (NTNU Social Research AS), Aage Mammen and Jostein Stavne-Johansen (Sogn and Fjordane University College), Kari Hoel Heldal (University of Agder), Thomas Dillens and Freddi Pedersen (University of Nordland), Sindre Mikael Dyrestad (University of Stavanger), Eva Maria Stø (Telemark University College), Ingeborg Barth-Vedøy (Norwegian School of Sport Sciences) and Pulmonary department at Oslo University Hospital, Ullevål.

Author Contributions

Conceived and designed the experiments: EE SAA. Performed the experiments: EE. Analyzed the data: EE EH SAA. Contributed reagents/materials/analysis tools: EE EH SAA. Wrote the paper: EE EH SAA. Contributed to the writing of the paper: EE EH SAA. Drafted the manuscript: EE.

References

Criteria for Maximum Effort during VO\textsubscript{2max
Paper III
Reduction in cardio-respiratory fitness after lung resection is not related to the number of lung segments removed

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Running Head: Cardio-respiratory fitness and lung cancer

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Abbreviation: CPET=cardiopulmonary exercise test, DLCO= Diffusion capacity of the lung for carbon monoxide, ERS/ESTS=European Respiratory Society/European Society for Thoracic Surgery, FEV1= Forced expiratory volume after 1 s, [Hb]=haemoglobin concentration, MVV=maximal voluntary ventilation, NSCLC= Non-Small-Cell lung cancer, SpO2= Oxygen saturation measured by pulse oximeter, ppo=predicted postoperative, VO2peak=peak oxygen uptake
ABSTRACT

Objectives: To evaluate the effect of lung cancer surgery on cardio-respiratory fitness (CRF) measured on a treadmill, and to assess the agreement between the predicted postoperative (ppo) and actually measured postoperative peak oxygen uptake ($\dot{V}O_{2\text{peak}}$).

Materials and Methods: Before and 4–6 weeks after lung cancer surgery, 70 patients (35 women) underwent measurements of pulmonary function and CRF via a cardio-pulmonary exercise test (CPET) until exhaustion. In addition, the 23 non-exercising patients underwent similar measurements after six months. Predicted postoperative (PPO) $\dot{V}O_{2\text{peak}}$ calculated from the number of functional segments removed was compared with the actually measured post-operative values of $\dot{V}O_{2\text{peak}}$ for accuracy and precision.

Results: After surgery, the $\dot{V}O_{2\text{peak}}$ decreased from 23.9±5.8 to 19.2±5.5 mL·kg$^{-1}$·min$^{-1}$ (-19.6±15.7%) ($P<0.001$). The breathing reserve increased by 5% ($P=0.001$); the oxygen saturation remained unchanged ($P=0.30$); the oxygen pulse decreased by 1.9 mL·beat$^{-1}$ ($P<0.001$); the haemoglobin concentration decreased by 0.7 gram·dL$^{-1}$ ($P=0.001$). The oxygen pulse was the strongest predictor for change in $\dot{V}O_{2\text{peak}}$; adjusted linear squared $r^2=0.77$. Six months after surgery, the $\dot{V}O_{2\text{peak}}$ remained unchanged (-3±15%, $P=0.27$).

The ppo $\dot{V}O_{2\text{peak}}$ (mL·kg$^{-1}$·min$^{-1}$) was 18.6±5.4 and the actually measured $\dot{V}O_{2\text{peak}}$ was 19.2±5.5 ($P=0.24$). However, the limits of agreement were large (CI:-7.4 to 8.2). The segment method miscalculated the ppo $\dot{V}O_{2\text{peak}}$ by more than ±10 and ±20% in 54% and 25% of the patients, respectively.

Conclusion: The significant reduction in $\dot{V}O_{2\text{peak}}$ and lack of improvement six months after lung cancer surgery cannot be explained by the loss of functional lung tissue, but appears to reflect a decrease in the patients’ cardiac function. Predicting postoperative $\dot{V}O_{2\text{peak}}$ based on
the amount of lung tissue removed is not recommendable due to poor precision.

ClinicalTrials.gov Identifier:NCT01748981

Keywords:
Cardiorespiratory fitness, non-small cell lung cancer, peak oxygen uptake, predicted postoperative function, surgery
1. Introduction

Globally, 1.61 million people are diagnosed with lung cancer each year, and the incidence is increasing.[1] The complications and mortality rate after surgery for this type of cancer are relatively high compared with other major surgical procedures and depend on the patient’s health prior to surgery and on the extent of the resection.[2] Therefore, pre-operative risk assessment and the ability to predict postoperative outcomes are of major clinical importance. Cardio-respiratory fitness (CRF) measured as peak oxygen uptake ($\dot{V}O_{2\text{peak}}$) has been reported as being a better predictor of postoperative complications and mortality than the traditionally used pulmonary function variables forced expiratory volume in the first second (FEV$_1$) and diffusing capacity for carbon monoxide (DL$_{CO}$).[3, 4] Consequently, current guidelines have recommended exercise testing and defined $\dot{V}O_{2\text{peak}}$ cut-off values for risk assessment.[5-7] Moreover, the European Respiratory Society/European Society for Thoracic Surgery (ERS/ESTS) guidelines include a modified version of the preoperative Bolliger algorithm,[8] in which $\dot{V}O_{2\text{peak}}$ is one of the pivotal measures. This algorithm has been validated, and was recently adjusted to lower thresholds,[9] thus allowing more patients to undergo surgery. In addition to predicted postoperative (ppo) FEV$_1$ and DL$_{CO}$, ppo $\dot{V}O_{2\text{peak}}$ is included in the algorithm. The ppo $\dot{V}O_{2\text{peak}}$ is based on the principle that the amount of resected functional lung tissue corresponds with the drop in $\dot{V}O_{2\text{peak}}$, regardless of whether a pulmonary limitation is present or not. However, $\dot{V}O_{2\text{peak}}$ is generally limited by cardiac output, and less by pulmonary factors,[10] which may question the validity of this ppo segment method.

In the few studies that have investigated the relationship between ppo $\dot{V}O_{2\text{peak}}$ and actually measured post-operative $\dot{V}O_{2\text{peak}}$, the sample size has been small,[11, 12] and the results have been conflicting.[12-15] Furthermore, the $\dot{V}O_{2\text{peak}}$ cut-off values and the agreement between ppo and actually measured $\dot{V}O_{2\text{peak}}$ values are based on exercise testing.
using a cycle ergometer instead of a treadmill. Leg discomfort during cycling is an important contribution to exercise termination in patients with lung cancer, rather than cardio-pulmonary limitation.[12, 13, 16, 17] This may explain the unexpectedly low peak heart rates [16, 18-20] and high breathing reserves (>40%) reported in previous studies [4, 12, 13]. When determining the degree of cardio-pulmonary reserve and ppo $\dot{V}O_{2peak}$, additional knowledge is thus warranted.

The objective of this study was to evaluate the effect of lung cancer surgery on cardio-respiratory fitness measured on a treadmill, and to assess the agreement between ppo $\dot{V}O_{2peak}$ and actually measured postoperative $\dot{V}O_{2peak}$.

2. Methods

This prospective study investigated 70 non-small-cell lung cancer (NSCLC) patients who underwent lung cancer surgery at the Oslo University Hospital or Akershus University Hospital in Norway from November 2010 to September 2012. Eligible patients were ≤ 80 years of age, had newly diagnosed or suspected NSCLC and had been accepted for surgery. Patients were not eligible if they were unable to perform a maximal exercise test on a treadmill. The majority of the included patients (n=61) were participants in a randomized controlled trial studying the effect of 20 weeks of exercise training starting 4-6 weeks after surgery.[21] The results of pre- to post surgery lung function and cardio-pulmonary exercise test (CPET) variables of that trial are included in this paper. In addition, the 6 months results of 23 patients who acted as non-exercising sedentary controls are also included in the current study (Figure 1).

The criteria used to determine operability were in accordance with the guidelines of the ERS/ESTS.[5] After signing an informed consent form, the patients were enrolled in the study and underwent lung cancer surgery through a muscle-sparing lateral thoracotomy or by video-
assisted thoracoscopic surgery (VATS). The study protocol was approved by the Regional Committee for Medical Ethics (REK Sør-Øst B, 2010/2008a) and registered in the ClinicalTrials.gov (NCT01748981).

2.1. Measurements

All patients received salbutamol and ipratropium bromide 30 min before the measurements. Among the patients who underwent measurements after 6 months, 33% received four cycles of adjuvant chemotherapy between the second and third measurement. None of the patients underwent organized exercise rehabilitation during the testing period.

Height and body mass were measured to an accuracy of 0.5 cm and 0.1 kg, respectively, with subjects wearing light clothes and no shoes; body mass index (BMI) was calculated as body mass/height$^2$ (kg/m$^2$).

Spirometry and DL$_{CO}$ were conducted according to guidelines (Vmax SensorMedics, Yorba Linda, CA).[22] Maximal voluntary ventilation (MVV) was measured directly by breathing as deep and frequent as possible for 12 seconds in standing position.

CPET was performed by uphill walking on a treadmill (Woodway, Würzburg, Germany) until exhaustion. All patients were familiar with treadmill walking before starting the test. Three minutes of warm-up and steady-state measurements were conducted with the treadmill speed individually set between 1.8 and 3.8 km·h$^{-1}$ and inclination set at 4% based on the predicted fitness level of the patients. The inclination was then increased each 60 s by 2%, up to 20%. If the participant was still able to continue, the speed was increased by 0.5 km·h$^{-1}$ until exhaustion. The test was terminated when the individual could no longer continue, even with encouragement. Gas exchange and ventilatory variables (V$E$) were measured continuously breath-by-breath while breathing into a Hans Rudolph two-way breathing mask.
The mask was connected to a metabolic cart (Vmax SensorMedics, Yorba Linda, CA) to assess the oxygen and carbon dioxide content in expired air to calculate oxygen uptake. HR was recorded each minute using a 12-lead ECG (Cardiosoft, GE Marquette Medical Systems, Milwaukee, WI).

A capillary blood sample was taken 60 s after test termination (ABL 700 series, Radiometer, Copenhagen, Denmark) for the measurement of haemoglobin- ([Hb]) and blood lactate concentration ([La']).

2.2. Data handling

The predicted values for FEV₁ and DL_{CO} were taken from the European Community for Steel and Coal.[23] The exercise variables were reported as a 30 s average and the $\dot{V}O_{2\text{peak}}$ was expressed as a percentage of predicted based on the equations of Edvardsen and colleagues.[24] The breathing reserve (%) was calculated using the following equation: 

$$\left(\frac{MVV - V_{E\text{peak}}}{MVV}\right) \times 100.$$ 

The oxygen pulse was calculated by dividing $\dot{V}O_{2\text{peak}}$ (in millilitres) by the peak heart rate (HR_{peak}). The actual extent of the operation (i.e., wedge resection, lobectomy or pneumonectomy) and number of lung segments removed were recorded after surgery, and the ppo $\dot{V}O_{2\text{peak}}$ was calculated using the remaining functional segment technique estimated by bronchoscopy, lung perfusion scan or computed tomography:

$$\text{ppo} = \frac{\text{preoperative value} \times (19 - n \text{ segments resected})}{19 - \text{unfunctional segments}}.$$ 

For patients who underwent wedge resection, a value of 1 was used per functional segment.
2.3 Statistical analysis

Data were analysed using IBM SPSS Statistical Data Editor, version 21.0. Results are presented as the mean ± standard deviation. Differences between pre- and post-surgery variables were analysed using Student’s paired t test.

Simple linear regression analyses were used to determine the relationship between the change from pre to post surgery values of different CPET variables (independent variables) and change in $\dot{V}O_{2peak}$ (dependent variable), and multiple linear regression analyses were used to study the contribution to the adjusted squared multiple correlation coefficient by including different sets of independent variables. Linear correlations ($r^2$) were reported between actually measured and ppo variables. In addition, linear regression was used to study the adjusted squared linear correlation between number of functional segments removed and per cent change in $\dot{V}O_{2peak}$.

The accuracy and precision of ppo vs actually measured values of pulmonary function and $\dot{V}O_{2peak}$ were determined, and the limits of agreement were calculated using a Bland–Altman plot with 95% confidence intervals. P values ≤0.05 were considered statistically significant.

3. Results

This study examined 35 women and 35 men undergoing lung cancer surgery (Table 1, Figure 1). The majority had adenocarcinoma (44%) and squamous cell carcinoma (39%), and 13 patients (19%) had stage IIIA disease.
Table 1. Baseline characteristics of the participants.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Participants (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>66.1±9.0</td>
</tr>
<tr>
<td>Range</td>
<td>35-80</td>
</tr>
<tr>
<td>BMI, kg·m⁻²</td>
<td>24.8±4.8</td>
</tr>
<tr>
<td>Health condition</td>
<td></td>
</tr>
<tr>
<td>COPD, No. (%)</td>
<td>26 (37)</td>
</tr>
<tr>
<td>Heart disease, No. (%)</td>
<td>20 (29)</td>
</tr>
<tr>
<td>Surgery procedure</td>
<td></td>
</tr>
<tr>
<td>Wedge/Lobectomy/Pneumonecetomy, n/n/n</td>
<td>2/56/12</td>
</tr>
<tr>
<td>Thoracotomy/VATS, n/n</td>
<td>59/11</td>
</tr>
<tr>
<td>Pulmonary function and physical characteristics</td>
<td></td>
</tr>
<tr>
<td>FEV₁, % of predicted</td>
<td>88.4±22.4</td>
</tr>
<tr>
<td>DLco, % of predicted</td>
<td>80.6±20.9</td>
</tr>
<tr>
<td>V̇O₂peak, % of predicted</td>
<td>80.6±16.4</td>
</tr>
<tr>
<td>V̇O₂peak, mL·kg⁻¹·min⁻¹</td>
<td>23.9±5.8</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or No. (%). BMI=Body Mass Index, calculated as body mass in kilogram divided by height in meters squared; COPD=Chronic Obstructive Pulmonary Disease; DLco=carbon monoxide lung diffusion capacity; FEV₁=forced expiratory volume after one second; VATS=Video Assisted Thoracic Surgery; V̇O₂peak=peak oxygen uptake. Def COPD=FEV₁/FVC<70% and FEV₁<80% of predicted.[25]

3.1 Physical characteristics before surgery

Pulmonary function and CPET variables before surgery are presented in Tables 1 and 2. The breathing reserve was 35.0±14.1%. The CRF of six patients (8%) was limited by their ventilatory capacity, defined as a breathing reserve <15%. At maximal effort during the CPET, the respiratory exchange ratio and [La] were 1.13±0.11 and 5.7±2.3 mmol·L⁻¹, respectively. Dyspnoea was the most frequent reason for stopping the exercise test (42%), followed by general exhaustion (23%) and leg exhaustion (23%).
3.2 Changes after surgery

After surgery, 11 patients did not undergo further investigation due to complications, metastases, or co-morbidities. For the remaining patients (n=59), change in pulmonary function and exercise variables following surgery are presented in Table 2. The $\dot{V}O_2\text{peak}$ decreased by $-5.0 \pm 4.5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (-19.6%) ($P<0.001$). However, nine patients did not exhibit a decrease in $\dot{V}O_2\text{peak}$ (Figure 2). Furthermore, the breathing reserve increased by $5.3 \pm 11.1\%$ ($P=0.001$); the oxygen saturation (SpO$_2$) remained unchanged ($P=0.30$); the oxygen pulse and haemoglobin concentration [Hb] decreased by $-1.9 \text{ mL}\cdot\text{beat}^{-1}$ ($P<0.001$) and $-0.7 \text{ gram}\cdot\text{dL}^{-1}$ ($P=0.001$), respectively.

**Table 2. Pulmonary function, cardiorespiratory fitness variables and haemoglobin concentration before and four to six weeks after surgery.**

<table>
<thead>
<tr>
<th></th>
<th>Before surgery</th>
<th>After surgery</th>
<th>Change from baseline (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lobectomy n=58</td>
<td>Pulmonectomy n=12</td>
<td>Lobectomy n=51</td>
</tr>
<tr>
<td>FEV$_1$, L</td>
<td>2.4±0.8</td>
<td>2.6±0.7</td>
<td>2.0±0.6</td>
</tr>
<tr>
<td>DLCO, mmol·min$^{-1}$·kPa$^{-1}$</td>
<td>6.7±2.1</td>
<td>7.2±2.3</td>
<td>5.5±1.6</td>
</tr>
<tr>
<td>$\dot{V}O_2\text{peak}$, mL·kg$^{-1}$·min$^{-1}$</td>
<td>23.4±5.5</td>
<td>26.2±6.9</td>
<td>19.5±5.4</td>
</tr>
<tr>
<td>$V_{E\text{peak}}$, L·min$^{-1}$</td>
<td>59.8±18.0</td>
<td>67.3±16.0</td>
<td>47.4±14.0</td>
</tr>
<tr>
<td>Breathing reserve, %</td>
<td>35.3±14.9</td>
<td>34.8±11.0</td>
<td>41.8±13.0</td>
</tr>
<tr>
<td>SpO$_2\text{peak}$, %</td>
<td>93.4±4.1</td>
<td>90.3±6.7</td>
<td>93.3±3.3</td>
</tr>
<tr>
<td>Oxygen pulse, mL·beat$^{-1}$</td>
<td>11.8±3.5</td>
<td>13.1±3.9</td>
<td>10.0±2.8</td>
</tr>
<tr>
<td>HR$_{\text{peak}}$, beat·min$^{-1}$</td>
<td>146.9±21.1</td>
<td>152.4±21.3</td>
<td>137.4±18.0</td>
</tr>
<tr>
<td>Haemoglobin, g·dL$^{-1}$</td>
<td>14.7±1.6</td>
<td>14.2±1.8</td>
<td>13.9±1.3</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. For pulmonary function, n=63 four to six weeks after surgery. CI=confidence interval; DLCO=carbon monoxide lung diffusion capacity; FEV$_1$=forced expiratory volume after one second; HR$_{\text{peak}}$=peak heart rate; SpO$_2$=oxygen saturation; $V_{E\text{peak}}$ = peak minute ventilation; $\dot{V}O_2\text{peak}$=peak oxygen uptake; *=Change from baseline is significant at the 0.01 level.
The oxygen pulse was the strongest predictor for change in $\dot{V}O_{2\text{peak}}$; adjusted linear squared $r^2=0.77$. Adding change in FEV$_1$, MVV, breathing reserve, DL$_{CO}$, peak SpO$_2$, and [Hb] in a multiple regression model, resulted in only a modest increase in the predicting value to an adjusted squared $r^2=0.83$, with DL$_{CO}$ as the second contributor.

In the patients who underwent measurements 6 months after surgery ($n=23$), the FEV$_1$ increased by $7\pm11\%$ ($P=0.002$), whereas the DL$_{CO}$ and $\dot{V}O_{2\text{peak}}$ remained unchanged compared with the measurement performed 4-6 weeks after surgery; $4\pm16\%$ ($P=0.36$) and $-3\pm15\%$ ($P=0.27$), respectively.

### 3.3 Predicted postoperative versus actually measured variables

The ppo $\dot{V}O_{2\text{peak}}$ was compared with the actually measured $\dot{V}O_{2\text{peak}}$ obtained 4–6 weeks after surgery (Table 3). There were no significant differences between the ppo and actually measured values (satisfactory accuracy); however, the limits of agreement were large (poor precision) (Figure 3). The linear correlation between ppo and measured VO$_{2\text{peak}}$ (in mL·kg$^{-1}$·min$^{-1}$) was $r^2=0.50$ ($P<0.001$) ($r^2=0.56$, $P<0.001$, for lobectomy and $r^2=0.15$, $P=0.187$, for pneumonectomy).

**Table 3.** Predicted postoperative (ppo) values and actually measured values 4–6 weeks after surgery for pulmonary function ($n=63$) and peak oxygen uptake ($n=59$) with limits of agreement and linear correlation ($r^2$).

<table>
<thead>
<tr>
<th></th>
<th>ppo value</th>
<th>Actually measured after surgery</th>
<th>Difference ppo-measured</th>
<th>P-value</th>
<th>Limits of agreement</th>
<th>Linear correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV$_1$, % of predicted</td>
<td>69.5±19.9</td>
<td>72.9±17.5</td>
<td>-3.4±13.7</td>
<td>0.06</td>
<td>-23.5 to 30.2</td>
<td>0.55</td>
</tr>
<tr>
<td>DL$_{CO}$, % of predicted</td>
<td>63.6±18.9</td>
<td>65.4±18.1</td>
<td>-1.7±12.3</td>
<td>0.27</td>
<td>-22.3 to 25.8</td>
<td>0.61</td>
</tr>
<tr>
<td>$\dot{V}O_{2\text{peak}}$, % of predicted</td>
<td>63.1±16.5</td>
<td>65.4±16.9</td>
<td>-2.3±13.3</td>
<td>0.20</td>
<td>-23.8 to 28.3</td>
<td>0.46</td>
</tr>
<tr>
<td>$\dot{V}O_{2\text{peak}}$, mL·kg$^{-1}$·min$^{-1}$</td>
<td>18.6±5.4</td>
<td>19.2±5.5</td>
<td>-0.6±4.1</td>
<td>0.24</td>
<td>-7.4 to 8.7</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. DL$_{CO}$=carbon monoxide lung diffusion capacity; FEV$_1$=forced expiratory volume after one second; $\dot{V}O_{2\text{peak}}$=peak oxygen uptake
Figure 3 demonstrates the poor relationship between the per cent change in actually measured $\dot{V}O_{2peak}$ from before to after surgery and the number of functional lung segments removed ($r^2=0.06$). The solid black line shows the calculated ppo $\dot{V}O_{2peak}$ using the recommended segment method, and demonstrates the large variance between calculated ppo- and actually measured values. By use of the segment method for predicting postoperative $\dot{V}O_{2peak}$, 32 patients (54%) were miss-predicted by $\geq\pm10\%$, and 15 patients (25%) were miss-predicted by $>\pm20\%$ (Figure 3).

4.0 Discussion

The purpose of this study was to evaluate the effect of lung cancer surgery on $\dot{V}O_{2peak}$ measured on a treadmill, and to assess the agreement between predicted and actually measured $\dot{V}O_{2peak}$ values. There was a clinically important[26] and significant reduction in $\dot{V}O_{2peak}$ after surgery, which lasted for more than 6 months. The reduction in $\dot{V}O_{2peak}$ cannot be explained by the number of lung segments removed. Even though the calculation of ppo $\dot{V}O_{2peak}$ was accurate, the precision of the ppo $\dot{V}O_{2peak}$ calculation was poor. Thus, the prediction of postoperative $\dot{V}O_{2peak}$ from the number of lung segments removed should be questioned.

4.1 Cardio-respiratory fitness

In the present study, the $\dot{V}O_{2peak}$ measured before surgery was $23.9\pm5.8\text{ mL\cdot kg}^{-1}\text{\cdot min}^{-1}$. Despite the inclusion of a high number of female patients (50%), this is, to our knowledge, the highest reported $\dot{V}O_{2peak}$ in a NSCLC population. In other studies reporting $\dot{V}O_{2peak}$ prior to surgery, the average value has varied between 11 and 20 mL\cdot kg$^{-1}$\cdot min$^{-1}$.[3, 11-15, 17, 18, 27] We do not have any indications of the Norwegian NSCLC population as being more fit than other populations. The age, body mass, level of pulmonary function and proportion of co-
morbidities are comparable with those of other NSCLC populations. Thus, the high $\dot{V}O_2$peak in our population might be explained by the test method. All studies mentioned above used exercise testing on a cycle ergometer, in contrast to our study using a treadmill. When cycling, quadriceps fatigue rather than cardio-pulmonary limitation is an important contributor to exercise limitation during CPET in patients with lung cancer.\[12, 13, 16, 17\] Furthermore, the heart rate reserve has been reported to be high when using cycle ergometer\[4\] and, consequently, the cardiopulmonary response to the increasing work rate may not have been fully challenged because of leg discomfort. These arguments are reflected in the significantly higher peak heart rate observed in the present study compared with other studies.\[12, 16, 18-20\] In addition, leg fatigue was only reported in 23% of the patients, which is considerably lower than that reported previously during cycling.\[12, 13, 16, 17\] Uphill walking is a more functional and dynamic exercise mode compared with cycling and generates more muscle mass activation, as recruitment of the quadriceps muscle is increased.\[28\] Simultaneously, it generates lower blood pressure and blood lactate accumulation, as well as higher cardiac output, giving a 10–20% higher $\dot{V}O_2$peak.\[28-30\] We therefore recommend treadmill testing for pre-operative measurement of physical fitness, enabling the patient to walk slowly up an increasingly steep incline until exhaustion. Preoperative measurement of $\dot{V}O_2$peak is recommended as a tool for risk stratification in all guidelines; ERS/ESTS,\[5\] British Thoracic Society,\[7\] and the American College of Chest Physicians.\[31\]

4.2 Effect of surgery

Four to six weeks after surgery, the $\dot{V}O_2$peak was decreased by 17% and 34% in patients who underwent lobectomy and pneumonectomy, respectively. Our results are fairly consistent with those of Nezu and colleagues.\[17\] In contrast, Brunelli and colleagues found a minimal
loss in $\dot{V}O_{2peak}$ (5%) measured 4 weeks after surgery, despite significantly larger decreases in $FEV_1$ and $DL_{CO}$.[32] However, the $\dot{V}O_{2peak}$ in that study was estimated from a symptom-limited stair-climbing protocol, using a non-validated equation, thus rendering comparison with the present study difficult.

The reduction in $\dot{V}O_{2peak}$ after surgery could not be explained by loss of lung tissue. This was demonstrated by the lacking relationship between the pre- to post-operative change in both $FEV_1$ and MVV and the change in $\dot{V}O_{2peak}$ and, in addition, by a rather unexpected increase in breathing reserve, defined as a difference between MVV and peak ventilation of less than 15%.[33] In fact, only two patients had their post-operative exercise capacity limited by lung mechanics. Furthermore, there was no change in $SpO_2$ during maximum exercise, even though $DL_{CO}$ at rest decreased significantly after surgery. These results are consistent with those of Hsia and colleagues, who found only a mild decline in arterial $O_2$ saturation during exercise after pneumonectomy, indicating high functional reserves for diffusion capacity in the lungs during exercise.[34] As cardiac output rises during incremental exercise in healthy subjects, a two-fold increase in diffusion capacity in the lungs is observed in order to maintain oxygenation,[35] indicating a higher diffusion capacity reserve compared with cardiac output. This may explain why the majority of patients undergoing lung resection are able to maintain their $SpO_2$ after surgery, even during maximal exercise.

Unfortunately, we did not measure stroke volume during exercise; however, the oxygen pulse, which yields information on the maximal cardiac stroke volume,[36-38] was significantly reduced after surgery. In fact, the oxygen pulse was the strongest predictor for the decrease in $\dot{V}O_{2peak}$. Normally, a low oxygen pulse reflects cardiac limitation if the patient does not desaturate,[39, 40] indicating a negative effect of surgery on the cardiac function. To confirm the impact on cardiac limitation, we in retrospect calculated the change in the
patients’ stroke volume by estimating the arterio venous oxygen difference,[39, 41] finding a
10 % reduction in the stroke volume (P<0.001) from before to after surgery (data not shown).

Anaemia is a factor that decreases the oxygen-carrying capacity of blood, thereby
affecting $\dot{V}O_{2\text{peak}}$ negatively.[42] According to the multiple regression analysis, the observed
decrease in [Hb] following surgery was not an important contributor to the decrease in $\dot{V}O_{2\text{peak}}$
following surgery. Loss of muscle mass may also reduce $\dot{V}O_{2\text{peak}}$. A previously reported, dual
energy X-ray absorptiometry scanning revealed a significant post-operative loss of muscle
mass in our patients.[21] Thus, the negative effect of surgery on both cardiac function and
muscle mass may have contributed to the post-operative decrease in $\dot{V}O_{2\text{peak}}$, while,
according to the lacking correlation with lung mechanics and the increase in breathing
reserve, the loss of lung tissue seems to be of less importance.

Prolonged sedentariness leads to a reduction in cardiac output, as well as muscle
wasting.[21, 43] This may explain the lack of increase in $\dot{V}O_{2\text{peak}}$ six months after surgery in
our group of non-exercising patients.[44] Regular high-intensity exercise training following
lung cancer surgery has, on the other hand, recently been shown to reverse these
conditions.[21] highlighting the importance of exercise rehabilitation in this group of patients.

4.5 Predicted postoperative $\dot{V}O_{2\text{peak}}$

The second aim of the current study was to evaluate the agreement between predicted
(ppo) and actually measured postoperative $\dot{V}O_{2\text{peak}}$ values during a maximal treadmill test in
patients undergoing lung cancer surgery. Estimation of ppo $\dot{V}O_{2\text{peak}}$ from the number of lung
segments removed is included in the ERS/ESTS guidelines for lung cancer surgery, in order
to predict surgical risk and functional outcome.[5] A ppo $\dot{V}O_{2\text{peak}}$ value <10 mL·kg$^{-1}$·min$^{-1}$ or
<35% of predicted is used as cut-off values for “high-risk patient”,[5] thus stressing the
importance of applying an accurate formula. Despite satisfying accuracy in ppo $\dot{V}O_{2\text{peak}}$
compared with actually measured $\dot{V}O_{2\text{peak}}$ after surgery, we found that the variance was large, indicating poor precision. This is in accordance with the lacking correlation between change in $\dot{V}O_{2\text{peak}}$ and the number of resected lung segments. In fact, the ppo $\dot{V}O_{2\text{peak}}$ value was miscalculated by more than $\pm20\%$ in as many as $25\%$ of the patients. The results regarding the agreement between ppo and actually measured values of $\dot{V}O_{2\text{peak}}$ in the present study are consistent with those of Brunelli and colleagues.[15] They concluded that the ppo $\dot{V}O_{2\text{peak}}$ was largely inaccurate and should be cautioned against,[15] a statement which is supported by our results.

5.0 Conclusions

The significant reduction in $\dot{V}O_{2\text{peak}}$ and lack of improvement six months after lung cancer surgery cannot be explained by the loss of functional lung tissue, but appears to reflect a decrease in the patients’ cardiac function. Predicting postoperative $\dot{V}O_{2\text{peak}}$ based on the amount of lung tissue removed is not recommendable due to poor precision.

Acknowledgements

The authors thank Christian Gartman, Vidar Søyseth (Akershus University Hospital), and Ahmed Rizwan Sadiq (Asker and Bærum Hospital Trust) for patient recruitment and Maria Arnesen, Marte Berget, Birgitte Birkeland and Silje Rustad for their expert lab assistance, and Ingar M Holme for excellent statistical guidance. Personnel at the Departments of Thoracic Surgery at Oslo University Hospital and Akershus University Hospital are acknowledged for their kind co-operation.
Contribution

EE, SAA, FB and OHS were responsible for the design and conduct of the study. EE, the guarantor of the paper, was responsible for patient recruitment, data collection, test-procedures and the statistical analysis. All authors contributed to the interpretation of data. EE drafted the manuscript, which was critically reviewed and approved by all authors.
Reference List


LEGEND TO FIGURES

Figure 1.
Flow of participants through the study. Measurements after exercise training are not included in the data analysis.

Figure 2.
Percent change in peak oxygen uptake (\( \dot{V}O_{2\text{peak}} \)) from before to after surgery for each patient relative to the number of functional lung segments removed. The solid line indicates the percent change in the calculated postoperative \( \dot{V}O_{2\text{peak}} \), using the segment method, \( \pm 10 \) per cent (dashed line) and \( \pm 20 \) per cent (dotted line).

Figure 3.
Relationship between the mean of actually measured and predicted postoperative oxygen uptake (ppo \( \dot{V}O_{2\text{peak}} \) in % of predicted) and the difference between the actually measured and ppo \( \dot{V}O_{2\text{peak}} \) with 95% confidence interval (1.96 SD).
Figure 1
Figure 2
Figure 3
Paper IV

Denne artikkelen ble tatt ut av den elektroniske versjonen av doktoravhandlingen i Brage på grunn av copyright-restriksjoner.
Artikkelen er tilgjengelig på: http://dx.doi.org/10.1136/thoraxjnl-2014-205944

This paper was removed from the electronic version of this PhD-thesis in Brage due to copyright restrictions.
The paper is available at: http://dx.doi.org/10.1136/thoraxjnl-2014-205944
Appendix 1

Part I

Approval from the Regional Committees for Medical Research Ethics

Approval from the Norwegian Social Science Data Services
S-08046b Kartlegging av fysisk aktivitetsnivå, helserelatert fysisk form og determinanter for fysisk aktivitet hos voksne og eldre i Norge [6.2008.142]

Søknad mottatt 08.01.08 med følgende vedlegg: Protokoll; informasjonsskriv med samtykkeerklæring; spørreskjema; følgerefleksjon til REK Sør-Ost datert 7. januar 2008.


Forskningsetisk vurdering

Denne studien er todelt, og vil kartlegge status for fysisk aktivitetsnivå, determinanter for fysisk aktivitet, fysisk form og variabler relatert til fysisk form blant den voksne og eldre delen av den norske befolkningen. Komiteen ser ingen etiske betenkeligheter ved denne studien, forutsatt at den direkte målingen av fysisk form/aerob kapasitet i undersøkelsens Del 2 gjennomføres slik den er beskrevet i prosjektbeskrivelsen (dvs. at screening foretas for testen og at akuttmedisinsk hjelp er tilgjengelig under testen).

Vi ber imidlertid prosjektgruppen om å revurdere utvalgsstørrelsen som ligger til grunn for undersøkelsens Del 1: Styrkebevegelsene som ligger til grunn for Del 1 og for Del 2) synes å hvile på et solid grunnlag. Vi er imidlertid at prosjektgruppen foretreter at hele 2/3 deler av de 6000 personene som blir forespurt sier seg villige til å delta i del 1 av studien. Dette synes svært optimistisk med utgangspunkt i at prosjektgruppen henviser til at responsraten ved nyttig gjennomførte landsdekkeende undersøkelser i regi av FHI har vært på om lag 50 %. Det er derfor besluttet å øke tallet til 8000 personer for å sikre et eit akselerometer i en periode på syv dager vil nok neppe bidra til å øke responsraten. Komiteen ønsker en refleksjon omkring hvorvidt dette er realistisk.

I prosjektets Del 2 foreslås det å utelate aldersgruppen 20-30 år pga. økonomiske hensyn. Et av prosjektets mer langsiktige målsettinger er å studere utviklingstrender innen ulike aldersgrupper, gjennom å gjenta undersøkelsen med jevne mellomrom. At den yngste aldersgruppen utelates er bekymringssfult da dette vil gjøre det problematisk å studere endringer i de yngste aldersgruppene over tid. Siden potensielt for forebygging sannsynligvis er størst i nettop de yngste aldersgruppene, vil utelatelsen redusere undersøkelsens verdier reddet for forebygging. Vi ber prosjektgruppen om å vurdere på nytt om ikke også denne aldersgruppen bør inkluderes.

Informasjonsskriv/samtykkeerklæring

1. Informasjonsskrivet må påføres logo.
2. I andre avsnitt på første side må det informeres at testen av fysisk form kan påføre enkelte noe ubehag da deler av denne skal utføres under hoy intensitet (flytt dette fram fra kapittel A).
3. Det må opplyses om at prosjektet er godkjent av Regional komité for medisinsk og helsefaglig forskningsetikk Helseregion Sør avdeling B, REK Sør B.

4. I kapittel A og B kan begrepsbruk være litt vanskelig å forstå. "Akselerometer" foreslås byttet ut med "aktivitetsmåler". Videre bør det forklares hva som ligger i at "eventuell utgifter for deltakerne i undersøkelsens del 2 vil bli dekket".

5. Dato for sletting av data/kode må angis.

6. "Dette vil ikke få konsekvenser for din videre må behandling" må utgå da personene som deltar i dette prosjektet ikke er til behandling som er knyttet til deltakelsen.

Vedtak
Prosjektet godkjennes under forutsetning av at de merknadene som er anført ovenfor blir innarbeidet før prosjektet settes i gang. Revidert informasjonskrav og samtykkeerklæring må sendes komiteen til orientering.

Komiteens avgjørelse var enstemmig.


Med vennlig hilsen

Tor Nørseth
Leder

Jorunn Lindholt
Sekreter
Professor Dr. scient Sigmund Alfred Anderssen
Norges idrettsløgskole
Ph. 4014 Ullevål Stadion
0806 Oslo

Regional komité for medisinsk og helsefaglig
forskningsetikk Sør-Ost B (REK Sør-Ost B)
Postboks 1130 Blindern
NO-0318 Oslo

Telefon: 22 85 06 70
Telefaks: 22 85 05 90
E-post: julianmk@medisin.uio.no
Nettadresse: www.etikkom.no

Dato: 29.04.08
Deres ref.: S-08046b
Vår ref.: S-08046b

S-08046b Kartlegging av fysisk aktivitetsnivå, helserelatert fysisk form og determinanter for fysisk aktivitet hos voksne og eldre i Norge [6.2008.142]

Vi viser til brev datert 18.03.08 vedlagt revidert informasjonsskriv og spørreskjema.

Komiteen tar revidert informasjonsskriv og spørreskjema til orientering.

Vi ønsker lykke til med prosjektet!

Med vennlig hilsen

Tor Nørseth
Leder

Julianne Krohn-Hansen
Sekretær
TILRÅDING AV BEHANDLING AV PERSONOPPLYSNINGER

Vi viser til melding om behandling av personopplysninger, mottatt 14.03.2008. Meldingen gjelder prosjektet:

18886  Kartlegging av fysiske aktivitetsnivå, helserelatert fysisk form og determinanter for fysisk aktivitet hos voksne og eldre i Norge
Behandlingsansvarig  Norges idrettsbhøgskole, ved institusjonens enerste leder
Dogali ansvarig  Sigmund A. Andersen

Personvernområdet har vurdert prosjektet, og finner at behandlingen av personopplysninger vil være regulert av § 7-27 i personopplysningsforskriften. Personvernområdet tar i bruk at prosjektet gjennomføres.

Personvernområdets tilrådning fortsetter at prosjektet gjennomføres i tråd med opplysningene gitt i meldesjenært, korrespondanse med ombudet, eventuelle kommentarer samt personopplysningsloven/-helseregisterloven med forskrifter. Behandlingen av personopplysninger kan settes i gang.


Vennlig hilsen

Bjørn Henrichsen
Solve Fauskevåg

Kontaktperson: Solve Fauskevåg tlf: 55 58 25 83
Vedlegg: Prosjektvurdering
Personvernombudet for forskning

Prosjektvurdering - Kommentar

18886

BAKGRUNN
Prosjektet er et samarbeid mellom institusjonene:
- Norges idretthøgskole
- Høgskolene i Finnmark, Bodo, Sogn og Fjordane, Vestfold, Telemark og Hedmark
- Universitetsene i Stavanger og Agder, samt NTNU

Norges idretthøgskole (NIH) er koordinerende aktør og databehandlingsansvarlig for prosjektet. Prosjektleder, ved NIH, er daglig ansvarlig. Det inngås databehandlingsavtale mellom samarbeidspartene i henhold til personopplysningsloven § 15.

FORMÅL
Formålet med undersøkelsen er å øke kunnskapen om fysisk aktivitetsnivå, fysiske aktivitetsvaner, samt determinanter for fysisk aktivitet i den voksne delen av den norske befolkningen.


UTVALG, INFORMASJON OG SAMTYKKJE
Utvalget er et tilfeldig utvalg av cirka 8000 personer. Utvalget trekkes fra Folkeregisteret og av EDB Business Partner basert på tillatelse fra Skattedirektoratet.

Utvalget sendes informasjonskrav og kan samtykke skriftlig til deltakelse.

DATAMATERIALET
Datamaterialet inneholder ved hjelp av spørreskjema, aktivitetsmåler og fysiske tester og målinger. Datamaterialet inneholder blant annet navn, personnummer, kjonn, alder, etniske bakgrunn, yrke, inntekt og ibrannsetting, kommunal, røyking og snus, medlemskap i idrettslag/foreninger, kosthold og bruk av TV og PC, fysisk form (balanse, styrke, bevegelighed og koordinasjon), høyde, vekt, livviktde, hoffviktde, kroppssammensetning, blodtrykk samt resultatene fra aktivitetsmåler (akselomenter) som utvalget skal gå med i syv dager.

REGISTRERING, OPPBEVARING OG UTLEVERING

Alle registrerte opplysninger tilknytter den delen av utvalget som ikke samtykker, anonymiseres umiddelbart etter at svarfristen på purringen har utløpt.

Prosjektleder vil ha tilgang til hele datamaterialet. De lokale koordinatørene har tilgang til den delen av datamaterialet som de er ansvarlige for å samle inn. Prosjektets styringsgruppe vil ikke ha tilgang til datamaterialet.


ANDRE TILLATELSER
Prosjektet er godkjent av Regional komité for medisinsk forskningssettikk Midt-Norge (REKs ref. S-08046b).
Skatteetaten har gitt tillatelse til å trekke utvalget inkludert noen bakgrunnsopplysninger fra Folkeregisteret (Skatteetatens ref. 2008/167522 /SKDRESF/G10 /341).

KOMMENTAR
Personvernombudet finner at prosjektet kan gjennomføres med hjemmel i personopplysningsloven (pol) §§ 8, første ledd og 9 a), samtykke.


Trekking og førstegangskontakt med utvalget kan hjemles i personopplysningsloven §§ 8 d) og 9 h). Det vises til at undersøkelsen er på oppdrag fra Sosial- og helsedirektoratet og tar sikte på å fremkalle ny representativ kunnskap om aktivitet og helse. Trekking og kontakt med et representativt utvalg kan vanskelig gjøres på mer skinsonn måte enn via Folkeregisteret. Ulempeene for de registrerte er minimale da de informeres om trekkingen, og registrerte opplysninger anonymiseres umiddelbart før de som ikke samtykker innen svarfrist for purringen har utløpt.
Appendix 2

Part I

Consent forms, Study information, test protocol and questionnaires
Forespørsel om deltagelse i Kan1
- en kartleggingsundersøkelse av fysisk aktivitet og fysisk form blant voksne og eldre
Hva er Kan1-undersøkelsen?
Kan1 er en landsomfattende kartlegging av befolkningens aktivitetsnivå og fysiske form. Vi har i dag ikke tilstrekkelig informasjon på dette feltet til å kunne beskrive utviklingstrekker i befolkningsssegmenter og geografiske områder og forskjeller mellom dem. Denne undersøkelsen er ett ledd i Helsedirektoratets Handlingsplan for fysisk aktivitet, hvor et av hovedmålene er å etablere et system for kartlegging av det fysiske aktivitetsnivået i befolkningen. Undersøkelsen gjennomføres over hele landet i løpet av 2008 og 2009 og utføres av følgende høyskoler og universiteter:

1. Høyskolen i Finnmark
2. Høyskolen i Bodø
3. NTNU Trondheim
4. Høyskolen i Sogn og Fjordane
5. Universitetet i Stavanger
6. Universitetet i Agder
7. Høyskolen i Telemark
8. Høyskolen i Vestfold
9. Norges idrettsfagskole
10. Høyskolen i Hedmark

Hva innebærer deltakelse i undersøkelsen for deg?
Deltakelse i undersøkelsen innebærer at du svarer på et spørreskjema og går med en aktivitetsmåler i syv dager. Aktivitetsmåleren er et lite og lett apparat som bæres i et elastisk belte rundt livet (se bilder neste side). Du går med måleren i 7 dager og returnerer den deretter sammen med spørreskjemaet i vedlagt returkonvolutt (Fase 1). I etterkant av Fase 1 vil om lag ¼ av deltakerne bli tilfeldig trukket ut og invitert til å gjennomføre en tilleggsundersøkelse av fysisk form (Fase 2). Du kan delta i den første delen av undersøkelsen, og si nei til videre deltakelse.

KAN du delta?
Velger du å delta i Kan1-undersøkelsen bidrar du med viktig og ny kunnskap om aktivitetsnivå og fysisk form i befolkningen.

Alle kan delta, unansett om man ser på seg selv som fysisk aktiv eller ikke.

Hensikten med undersøkelsen er å kartlegge et utvalg som representerer hele befolkningen, ikke bare den delen som er mest aktiv.

Fordeler og ulemper

Hva skjer med informasjonen om deg?
All informasjon som samles inn om deg, vil bli behandlet i henhold til gjeldende lover og forskrifter. Alle medarbeidere involvert i undersøkelsen har taushetsplikt, og opplysningene som samles inn, vil kun bli brukt til godkjente forskningsformål. Se avsnittet om personvern på neste side for mer informasjon.

Frivillig deltakelse
Det er frivillig å delta i undersøkelsen. Du kan når som helst trekke deg uten å oppgi noen grunn. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side.
Kriterier for deltakelse
Kriterier for deltakelse er at man er over 20 år, bor i Norge og er norsk statsborger.

Tidsplan
I perioden april til november 2008 sendes spørreskjema og aktivitetsmåler til deltakeren. Denne delen av undersøkelsen skjer kun per post og kalles Fase 1. Et tilfeldig utvalg av deltakerne i Fase 1 (omtrent ¼) vil bli invitert til en undersøkelse av fysisk form (Fase 2). Fase 2 vil finne sted to til seks måneder etter hovedundersøkelsen. Det er fullt mulig å si nei til deltakelse i Fase 2, selv om man har deltatt i Fase 1.

Mulige bivirkninger
Det er ingen kjente bivirkninger ved deltakelse i undersøkelsen. Test av fysisk form i Fase 2 kan påføre deltaker noe ubeheg idet man skal utføre enkelte øvelser med høy intensitet. Eventuelle reiseutgifter for deltaker som blir invitert til deltakelse i Fase 2, vil bli dekket av undersøkelsen.

Personvern
Undersøkelsen er godkjent av Regional komité for medisinsk og helsefaglig forskningsetikk Helseregion Sør avdeling B, REK Sør B. Undersøkelsen er tilrådd av personvernombudet for forskning, Norsk samfunnsvitenskapelig datatjeneste A/S.

Opplysninger som registreres om deg, er personalia som alder, kjønn, sivil status og etnisitet, i tillegg til opplysninger om blant annet aktivitet, kosthold og helse. Du kan være trygg på at informasjonen du bidrar med til undersøkelsen, vil bli behandlet med respekt for personvern og privatliv, og i samsvar med lover og forskriver.

Innsamlede opplysninger oppbevares slik at navn er erstattet med en kode som viser til en atskilt navneliste. Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Det vil ikke være mulig å identifisere deg i resultatene av undersøkelsen når disse publiseres.

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


Økonomi og Helsedirektorats rolle
Undersøkelsen er finansiert og initiert av Helsedirektoratet.

Bilde 1 og 2. Aktivitetsmåleren i bruk
Samtykke til deltakelse i undersøkelsen

Dette eksemplaret underskrives og returneres i vedlagt svarkonvolutt. Den returnerte samtykkeerklæringen vil bli oppbevart på ett nedlåst sted.

Jeg er villig til å delta i undersøkelsen

Vennligst fyll ut opplysningene nedenfor:
(skriv tydelig, helst med blokkbokstaver)

Fornavn:

……………………………………………………………………………………………………………………………………………………………………

Etternavn:

……………………………………………………………………………………………………………………………………………………………………

……………………………………………………………………………………………………………………………………………………………………

(Signer her)

Jeg bekretter å ha gitt informasjon om undersøkelsen

Professor Sigmund Alfred Anderssen
Prosjektleder
Seksjon for idrettsmedisin
Norges idrettshøgskole
Invitasjon til deltakelse i kartleggingsundersøkelsen, fase 2

Tusen takk for din deltakelse i fase 1 av kartleggingsundersøkelsen hvor du gikk med aktivitetsmål og svarte på spørreskjema. Vi inviterer deg nå til videre deltagelse i undersøkelse ved å møte til en personlig helseundersøkelse ved STED.

Hva går undersøkelsen ut på?
Undersøkelsen inneholder ulike deler, blant annet måling av:

- hjerte- og lungefunksjon
- blodtrykk i hvile og under aktivitet
- kartlegging av fysisk form

I tillegg skal du gjennomføre enkle øvelser som kartlegger balanse, styrke og bevegelighet.

Undersøkelsen tar totalt ca 1 1/2 time.

Hvorfor delta?
- Undersøkelse av egen helse
- Forebygging av fremtidige helseproblemer
- Du gjør en viktig innsats for forskning

Alle er like viktige!
Det er viktig at flest mulig deltar i helseundersøkelsen. Undersøkelsen passer for alle personer, uansett alder og funksjonsnivå. Undersøkelsen tilpasses den enkelte deltaker og man gjennomfører kun de målingene man selv ønsker. Hver deltaker er like viktig, uansett om man er ung eller gammel, trent eller utrent.

Tilbakemelding
Resultatene vil i etterkant gjennomgåes med deg i forhold til helsestatus og fysisk form.

Du vil også få tilbakemelding på resultatene fra ukken du gikk med aktivitetsmål.
Praktiske opplysninger

En representant fra testセンターet vil om kort tid ta kontakt per telefon for å svare på spørsmål, og eventuelt avtale et tidspunkt for helseundersøkelsen. Etter telefon- samtalen vil du motta skriftlig bekreftelse på oppmøtetid og tidspunkt.


Litt informasjon om de ulike del-undersøkelsene

Lungefunksjon
Du skal puste så hardt du klarer i et apparat. Mengde luft som blåses ut er et mål på hvordan lungene fungerer.

Blodtrykk
Blodtrykk måles manuelt på overarmen i hvile og under aktivitet. Høytt blodtrykk er en viktig risikofaktor for hjerte- og karsykdom.

Utholdenhet
Utholdenhet måles ved gange på tredemølle. Undervisingsanalyseres utåndingsrasser og du får et mål på kondisjon.

Bevegelselighet og styrke
Til slutt i undersøkelsen gjennomføres enkle øvelser som registrerer balanse, styrke og bevegelselighet. Eksempler er måling av gripstyrke i hånd og bevegelselighet i nakke og skulder.

Hva brukes opplysningene til?
Opplysningene fra undersøkelsen vil kun brukes til forskning og det vil ikke være mulig å identifisere enkeltpersoner ut ifra resultatene.

Ta kontakt!
Dersom du lurer på noe, ta kontakt:

ABC
Kontor: 55 55 55 55
Mobil: 55 55 55 55
E-post: abc@mail.no

ABC
Mobil: 55 55 55 55
E-post: abc@mail.no

Det kan være at vi har forsøkt å ringe deg uten å lykkes. Dersom du ikke hører noe fra oss innen 14 dager, vennligst ta kontakt!

Vi sees på STED
Egenerklæringsskjema Kan1, fase 2

Skjemaet fylles ut av alle som skal delta i fysisk test i fase 2 av kartleggingsundersøkelsen Kan1.

Alt. 1. Skjemaet returneres utfylt til følgende adresse så snart som mulig:  
Alt. 2. Skjemaet fylles ut på testdag, i forkant av testing  
Adresse  
Adresse

<table>
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<th>Etternavn:</th>
<th>Fornavn:</th>
<th>Født:</th>
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<th>E-mail adresse:</th>
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<tr>
<th>Dine idretts- og mosjonsvaner:</th>
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<td>JA</td>
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☐ ☐ 1. Mosjonerer du regelmessig med lettere kondisjonsaktiviteter (f.eks gåturer, lett jogging)?

☐ ☐ 2. Driver du regelmessig hardere kondisjonstrening og/eller konkurrer i kondisjonssidretter?
<table>
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<th>JA</th>
<th>NEI</th>
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<tr>
<td></td>
<td>1. Kjenner du til at du har en hjertesykdom?</td>
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<tr>
<td></td>
<td>2. Hender det du får brystsmerter i hvile eller i forbindelse med fysisk aktivitet?</td>
</tr>
<tr>
<td></td>
<td>3. Kjenner du til at du har høyt blodtrykk?</td>
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<tr>
<td></td>
<td>4. Bruker du for tiden medisiner for høyt blodtrykk eller hjertesykdom (f.eks. vanndrivende tabletter)?</td>
</tr>
<tr>
<td></td>
<td>5. Har noen av dine foreldre, søsken eller barn fått hjerteinfarkt eller dødd plutselig (før fylte 55 år for menn og 65 for kvinner)?</td>
</tr>
<tr>
<td></td>
<td>6. Røyker du?</td>
</tr>
<tr>
<td></td>
<td>7. Kjenner du til om du har høyt kolesterolnivå i blodet?</td>
</tr>
<tr>
<td></td>
<td>8. Har du besvimt i løpet av de siste 6 måneder?</td>
</tr>
<tr>
<td></td>
<td>9. Hender det du mister balansen på grunn av svimmelhet?</td>
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<tr>
<td></td>
<td>10. Har du sukkersyke (diabetes)?</td>
</tr>
<tr>
<td></td>
<td>11. Kjenner du til noen annen grunn til at din deltakelse i prosjektet kan medføre helse- eller skaderisiko?</td>
</tr>
</tbody>
</table>

Gi beskjed straks dersom din helsesituasjon forandrer seg fra nå og til undersøkelsen er ferdig.

Dine eventuelle kommentarer til spørsmålene eller andre relevante opplysninger om egen helsesituasjon med tanke på å gjennomføre fysiske tester:

__________________________________________________

Sted og dato

__________________________________________________

Underskrift
Protokoll belastningstest, fase 2

Besøket på testrestaurant foregår over en dag og starter med utfylling av egenklæringsskjøtta, måling av blodtrykk, høyde og vekt før belastning på tredemølle gjennomføres ved måling av maksimal oksygenoptok.

Testene gjennomføres under samme atmosfæriske og klimatiske betingelser, dvs normal værelsetemperatur (18-24 grader C) og relativ luftfuktighet (30-60 %).

Høyde og vekt
Høyde måles til nærmeste hele cm mens forskjepersonen står opprett i tittell en vegg uten sko. FP står med hælene sammen bak helt inn til veggens. Blikket er rettet forover med rett og støtt hode.
FP vekt måles til nærmeste 0,1 kg på en kalibrert vekt, hvor FP er iført kun lett buksel og lett skjorte. Ca-vekt på klærplagg trekkes fra (0,3 kg for t-skjorte og kortbuksle).

Måling av blodtrykk i hvile
Blodtrykk måles manuelt i sittende avslappet stilling ved et spesialutstyr (Rieaer, Big Ben, Tyskland) minimum to ganger på høyre arm. Begge målenter noteres i CRF. Et blodtrykk > 150/110 mmHg før start fører til eksklusjon fra belastningsundersøkelsen og forskjepersonen (FP) informeres om misforstår eller hypertensjon.

Belastning på tredemølle
Etter måling av blodtrykket starter forberedelser til arbeidsbelastningen. Patien ten har på forhånd hatt individuell tilvenning på tredemøll en før å sikre best mulig teknik med så normal gange som mulig. Met ikke i øvre ledninger av å anstrengse seg til utmattelse.

Protokollen på tredemøllen er en gående ramp protokoll med konstant hastighet og progressiv økende hølvende vinkel (2 %) hvert minutt (Fig 1). Alle FP starter på samme
arbeidsbelastning avhengig av alder: < 55 år på 4.8 km/t og ≥ 55 år på 3.8 km/t. For de sprøkkede vit hastigheten økte med ca 0.5 km/t hvert minutt etter at hengselsvinkelen har passert 20%. BORG-skala forklarer grundig før start og registeres hvert 3. minutt under belastningsundersøkelsen. Hjertefrekvensen måles kontinuerlig ved hjelp av pulslokke (Polar, Finland eller EKG) og registeres hvert minutt til utmattelse. Ett min etter endt test tøres en kapillærprøve for bestemmelse av blodaktat for vurdering av grad av utmattelse.

![Diagram](image)

**Figur 1.** Eksempl på fremstilling av mobilisert balanseprotokoll for braksepersoner < 55 år, med de ulike testfase; rest (1), độodby stikk (2), test (3) og recovery (4). Hastighet, hengselsvinkel og belastning (skilt) er angitt i fargen som blått, grønt og granitt.

**Videre følger:**

- Oversikt over hastighet og hengselsvinkel ved de to ulike protokollene, for programmering av protokoll på tredemell
- Flytteskema over hele testprosedyren i forhold til alder og risiko er angitt i vedlegg 3 og 4, og bør være tilgjengelig i nærheten av tredemell'en under undersøkelsen
- Borgs skala med forklaring
**Testprotokoll på tredemølle (alder < 55 år)**
Modifisert Balke protokoll

<table>
<thead>
<tr>
<th>Trinn</th>
<th>Antall minutter</th>
<th>Stigningsgrad (%)</th>
<th>Hastighet (km/t)</th>
<th>VO₂ måling</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>4</td>
<td>4,8</td>
<td>Ja</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>6</td>
<td>4,8</td>
<td>Ja</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>8</td>
<td>4,8</td>
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</tr>
<tr>
<td>4</td>
<td>1</td>
<td>10</td>
<td>4,8</td>
<td>Ja</td>
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<tr>
<td>5</td>
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<td>12</td>
<td>4,8</td>
<td>Ja</td>
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<tr>
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<td>7</td>
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<td>16</td>
<td>4,8</td>
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<tr>
<td>8</td>
<td>1</td>
<td>18</td>
<td>4,8</td>
<td>Ja</td>
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<tr>
<td>9</td>
<td>1</td>
<td>20</td>
<td>4,8</td>
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<td>20</td>
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<tr>
<td>21</td>
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<td>10,3</td>
<td>Ja</td>
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</table>
## Testprotokoll på tredemølle (alder ≥ 55 år)

Modifisert Balke protokoll

<table>
<thead>
<tr>
<th>Trinn</th>
<th>Antall minutter</th>
<th>Svingingsgrad (%)</th>
<th>Hastighet (km/h)</th>
<th>VO2 måling</th>
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<tbody>
<tr>
<td>Tilværing</td>
<td>2 - 7</td>
<td>0</td>
<td>2,0 - 4,0</td>
<td>Nei</td>
</tr>
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<td>3,8</td>
<td>Ja</td>
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<tr>
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<td>3,8</td>
<td>Ja</td>
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<tr>
<td>3</td>
<td>1</td>
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<td>3,8</td>
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<td>4</td>
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<tr>
<td>6</td>
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<td>14</td>
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<tr>
<td>7</td>
<td>1</td>
<td>16</td>
<td>3,8</td>
<td>Ja</td>
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<tr>
<td>8</td>
<td>1</td>
<td>18</td>
<td>3,8</td>
<td>Ja</td>
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<tr>
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<tr>
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<td>20</td>
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<tr>
<td>17</td>
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<td>20</td>
<td>6,8</td>
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</tr>
<tr>
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<td>20</td>
<td>8,3</td>
<td>Ja</td>
</tr>
<tr>
<td>21</td>
<td>1</td>
<td>20</td>
<td>8,8</td>
<td>Ja</td>
</tr>
</tbody>
</table>
Flyttskjema ved maksimal arbeidsbelastning med lav risiko

1. Ønsk velkommen og forklar kort hensikt og prosedyren
2. Egenklæringsskjema fylles ut og gjennomgås
3. Mål blodtrykk sittende i hvile minimum to ganger på høyre arm. Noter ned laveste sys og dia trykk. Eksekluder FP med BT > 180/110mmHg
4. Mål høyde uten sko og noter til nærmeste hekse cm. Hæl og hode inntil vegg med blikket rettet fremover
5. Register vekst først lett treningsøy ut sko og noter til nærmeste 0.1 kg. Trekk fra ca vekt før tre (shoarts + T-shirt ca 0.3 kg)
6. Paimonter pulssaks og kontroller gode signaler med regelmessig frekvens
7. Start tilværelse på tredemønster på ca 3 km/t. FP forsøker i starten kun å holde seg fast med én hånd, før dere etter å slippe. Oppmuntrer til å gå i ikke mangjøre. Øk gradvis til 4.8 km/t
8. Skriv inn inititul, fodselsdato, personkode, høyde og vekst i software mens tilværelse pågår
   Kontroller for lekkasje. Forklaret grundig prosedyren på tredemønsten mens pasienten puster i masken, gi et estimat på grad av utmattelse, og avklar prosedyre for slutt
11. Start belastningsundersøkelsen og fullfør til utmattelse (BORG>16, tilfredsstillende utmattet vurdert av testleder)
12. Neder HF hvert minutt og BORG hvert 3. minutt i software
13. Ved svimmelhet, brytsmerter, urelhet, og signifikant, avbryt umiddelbart, og
14. Spør BORG skal umiddelbart etter slutt, og be FP angi hvorfor slutt; muskulært utmattet, pust, generell utmattelse
15. Monter av maska, sikre venstres tilbakestrømming med let "tripping" på tredemønsten
16. Mål blodtrykk med fingersikk 1 min etter avsluttet test
17. Avslutt, gå av tredemønsten og forklar kort resultatet. Opprethold bevegelse i underkjemnitten.
Flytskjema ved maksimal arbeidsbelastning med moderat risiko

> 44 år og > 54 år eller de med mer enn 2 risikofaktor avgirings på skjema

1. Ønsk veikommen og forklar kort hensikt og prosedyren ved dette besøket
2. Egenklaringskjema fylles ut og gjennomgås sammen med FP. Ta enkel
   anamnese vedt anstrengelse/fysisk aktiviteitsnivå og vurder om test skal
   gjennomføres
3. Må blodtrykk sittende i hul på høyre arm minimum to ganger. Noter ned laveste
   sva og dia trykk. Ekstendag FP med BT > 180/110mmHg
4. Mål hoyde uten sko og noter til nærmeste hele cm. Hæl og hode inni vegg med
   blikket rettet fremover
5. Registerer vekt iført lett treningsøyde uten sko og noter til nærmeste 0.1 kg. Trekk fra
   ca vekt for tøy (shorts = T-shorte ca 0.3 kg)
6. Evt barber og monter på EKG-elektroder (minimum tre elektroder). Sikre ledninger
   for støy med tape og kontroller signaler og regelmessig ryttre
7. Fortsett fra pkt 7 – 17 på Flytskjema “Lav risiko”

Flytskjema ved maksimal arbeidsbelastning med høy risiko

> 44 år og > 54 år eller de med mer enn 2 risikofaktor avgirings på skjema

Protsydren som “med moderat risiko” samt lege tilgjengelig under
undersøkelsen. Undersøkelsesidspunktet avtales helst på spesielle dager.
<table>
<thead>
<tr>
<th>Nummer</th>
<th>Beskrivelse</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Ingen belastning overhode</td>
</tr>
<tr>
<td>7</td>
<td>Ekstremt lett</td>
</tr>
<tr>
<td>8</td>
<td>Veldig lett</td>
</tr>
<tr>
<td>9</td>
<td>Lett</td>
</tr>
<tr>
<td>10</td>
<td>Noenlunde hardt</td>
</tr>
<tr>
<td>11</td>
<td>Hardt (tungt)</td>
</tr>
<tr>
<td>12</td>
<td>Veldig hardt</td>
</tr>
<tr>
<td>13</td>
<td>Ekstremt hardt</td>
</tr>
<tr>
<td>14</td>
<td>Maksimal utmattelse</td>
</tr>
</tbody>
</table>
Forklaring til BORG skala

"Tallet 6 er det letteste du noen gang har opplevd – du føler du nærmest svever av sted".

"Ved tallet 15 er du ganske andpusten, det begynner å føles ubehagelig, og du har problemer med å føre en samtale".

"Tallet 20 er derimot det mest anstrengende og sittsomme som finnes i hele verden. Så sliten har du kanske aldri vært før. Du har da vært i krigen i to uker og må ligge og hvile i minst 30 min etterpå. Så sliten er det ikke meningen at du skal bli i dag".
Kjære Kan1 deltaker,

Ved hjelp av besvarelsen fra deg og andre deltakere vil vi få økt kunnskap om det fysiske aktivitetsnivået i den norske befolkning. I tillegg vil vi få bedre forståelse for hvilke forhold som er knyttet til fysisk aktivitet blant voksne og eldre.

Du har selvsagt anledning til å unnlate å svare på enkeltspørsmål. Det er imidlertid viktig at du gir ærlige svar. Informasjonen i dette spørreskjemaet behandles konfidensielt og ditt navn vil verken forekomme i datafiler eller i skriftlig materiale.


Skjemaet skal leses ved hjelp av en datamaskin. Bruk sort eller blå penn ved utfylling. Det er viktig at du fyller ut skjemaet riktig:

• Ved avkrysning, sett ett kryss innenfor rammen av boksen ved det svaralternativet som passer best

X Riktig
☐ X Galt
☐ ☐ Om du krysser av i feil boks, retter du ved å fylle boksen slik

• Skriv tydelige tall innenfor rammen av boksen

7 4 Riktig
4 7 Galt

• Bruk blokkbokstaver hvis du skal skrive A B C D E F

På forhånd takk for hjelpen!
### Bakgrunnsinformasjon

1) **Kjønn:**  
- [ ] Kvinne  
- [ ] Mann  

2) **Fødselsår:** 19  

3) **Høyde:** [ ] cm  
4) **Vekt:** [ ] kg  

5) **Hvilken utdanning er den høyeste du har fullført?** (Sett ett kryss)  
- [ ] Mindre enn 7 år grunnskole  
- [ ] Grunnskole 7-10 år, framhaldsskole eller folkehøgskole  
- [ ] Realskole, middelskole, yrkesskole, 1-2 årig videregående skole  
- [ ] Artium, økonomisk gymnas, allmennfaglig retning i videregående skole  
- [ ] Høgskole/universitet, mindre enn 4 år  
- [ ] Høgskole/universitet, 4 år eller mer  

6) **Hva er din hovedaktivitet?** (Sett ett kryss)  
- [ ] Yrkesaktiv heltid  
- [ ] Yrkesaktiv deltid  
- [ ] Arbeidsledig  
- [ ] Hjemmeværende  
- [ ] Pensjonist/trygdet  
- [ ] Student/militærtjeneste  

7) **Hvor høy var husholdningens samlede bruttoinntekt siste år?** (sett ett kryss)  
   Ta med alle inntekter fra arbeid, trygder, sosialhjelp og lignende  
- [ ] Under 125.000 kr  
- [ ] 125.000 – 200.000 kr  
- [ ] 201.000 – 300.000 kr  
- [ ] 301.000 – 400.000 kr  
- [ ] 401.000 – 550.000 kr  
- [ ] 551.000 – 700.000 kr  
- [ ] 701.000 – 850.000 kr  
- [ ] Over 850.000 kr  
- [ ] Ønsker ikke svare
8) Hvor mange innbyggere er det i din bostedskommune? (sett ett kryss)
- Under 1000
- 1001 – 5000
- 5001 – 10.000
- 10.001 – 20.000
- 20.001 – 30.000
- 30.001 – 100.000
- Mer enn 100.000

9) Hvordan vurderer du din egen helse sånn i alminnelighet? (sett ett kryss)
- Meget god
- God
- Verken god eller dårlig
- Dårlig
- Meget dårlig

10) I hvilken grad begrenser din helse dine hverdagslige gjøremål? (sett ett kryss)
- I stor grad
- I noen grad
- I liten grad
- Ikke i det hele tatt

11) Mener du at fysisk aktivitet er viktig for å kunne vedlikeholde egen helse? (sett ett kryss)
- Ja, meget viktig for meg
- Egentlig tenker jeg ikke så mye på det
- Nei, det er ikke så viktig for meg

12) Har du, eller har hatt: (sett gjerne flere kryss)
- Astma
- Kronisk bronkitt/emfysem/KOLS
- Hjerteinfarkt
- Angina Pectoris (hjertekrampe)
- Hjerneslag/hjerneblødning ("drypp")
- Kreft
- Spiseforstyrrelser
- Allergi
- Psykiske plager du har søkt hjelp for
- Sukkersyke (diabetes type I)
- Sukkersyke (diabetes type II)
- Benskjørhet/osteoporose
- Revmatiske lidelser

Annet: ______________________________________________________________
Fysisk aktivitet

De neste spørsmålene omhandler fysisk aktivitet. Fysisk aktivitet omfatter både:

- fysisk aktivitet i hverdagen (i arbeid, fritid og hjemme, samt hvordan du forflytter deg til og fra arbeid og fritidssyssler)
- planlagte aktiviteter (gå på tur, svømming, dansing)
- trening (for å bedre kondisjon, muskelstyrke og andre ferdigheter)

Det er flere nesten like spørsmål - det er meningen

13) Er du **aktivt medlem** av et idrettslag eller en idrettsklubb? (sett ett kryss)
   - [ ] Ja
   - [ ] Nei, men jeg har vært medlem før
   - [ ] Nei, jeg har aldri vært medlem (gå til spm 15)

14) Når ble du medlem for første gang?
   
   Jeg ble medlem da jeg var __________ år gammel

15) Dersom du er fysisk aktiv, hvilke aktiviteter driver du vanligvis med:
   (Sett gjerne flere kryss)

   - [ ] Turgåing  
   - [ ] Dans  
   - [ ] Golf  
   - [ ] Langrenn  
   - [ ] Yoga/pilates  
   - [ ] Tennis  
   - [ ] Ballspill  
   - [ ] Stavgang  
   - [ ] Svømming  
   - [ ] Vanngymnastikk  
   - [ ] Alpint/snowboard  
   - [ ] Kampsport (karate, judo ol)  
   - [ ] Squash/Badminton/Bordtennis  
   - [ ] Padling/roing  
   - [ ] Sykling/spinning  
   - [ ] Jogging  
   - [ ] Skøyter/bandy/hockey  
   - [ ] Trening til musikk i sal  
   - [ ] Annet, hva:  

   - 3 -
16) Hvor ofte trener du på de måtene som er nevnt under?
(Sett ett kryss for hvor ofte du er aktiv på hver måte)

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<th>Måte</th>
<th>Aldri</th>
<th>Sjelden</th>
<th>1-3 g/mnd</th>
<th>1 dag/uke</th>
<th>2-3 dag/uke</th>
<th>4-6 dag/uke</th>
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<td>På jobben eller skolen…</td>
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<td></td>
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</tr>
<tr>
<td>I svømmehall…………</td>
<td></td>
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</tr>
<tr>
<td>Sykler………………..</td>
<td></td>
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</tr>
<tr>
<td>Danser………………..</td>
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<tr>
<td>Skitur……………….</td>
<td></td>
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<tr>
<td>Fottur……………….</td>
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</tr>
</tbody>
</table>

17) Hvor mange timer den siste uken har du vært i fysisk aktivitet i hjemmet eller i tilknytning til hjemmet? Det er kun aktiviteter som varer i minst 10 minutter i strekk som skal rapporteres

<table>
<thead>
<tr>
<th>Aktivitet</th>
<th>Ingen</th>
<th>&lt; 1 time</th>
<th>1-2 timer</th>
<th>3-4 timer</th>
<th>&gt; 4 timer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lett aktivitet - ikke svett/andpusten…</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hard aktivitet - svett/andpusten…………</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
18) Angi bevegelse og kroppslig anstrengelse i din fritid. Hvis aktiviteten varierer megen f.eks mellom sommer og vinter, så ta et gjennomsnitt. Spørsmålet gjelder bare det siste året (sett ett kryss i den ruta som passer best)

- Lese, ser på fjernsyn eller annen stillesittende beskjedtelse?…………………………………
- Spaserer, sykler eller beveger deg på annen måte minst 4 timer i uka?
  (Her skal du regne med gang eller sykling til arbeidsstedet, søndagsturer mm)………………………….
- Driver mosjonsidrett, tyngre hagearbeid e.l?
  (Merk at aktiviteten skal vare minst 4 timer i uka)………………………………………………………….
- Trener hardt eller driver konkurranseidrett regelmessig og flere ganger i uka……..

Når du svarer på spørsmålene 19 - 22:

**Meget** anstrengende – er fysisk aktivitet som får deg til å puste **mye mer enn vanlig**

**Middels** anstrengende – er fysisk aktivitet som får deg til å puste **litt mer enn vanlig**

Det er kun aktiviteter som varer **minst 10 minutter i strekk** som skal rapporteres

19a) Hvor mange dager i løpet av de siste 7 dager har du drevet med **meget anstrengende** fysiske aktiviteter som tungt løft, gravearbeid, aerobics eller sykle fort? Tenk bare på aktiviteter som varer **minst 10 minutter i strekk**

- Dager per uke
- Ingen (gå til spørsmål 20a)

19b) På en vanlig dag hvor du utførte **meget anstrengende** fysiske aktiviteter, hvor lang tid brukte du da på dette?

- Timer
- Minutter
- Vet ikke/husker ikke

20a) Hvor mange dager i løpet av de siste 7 dager har du drevet med **middels anstrengende** fysiske aktiviteter som å bære lette ting, sykle eller jogge i moderat tempo eller mosjonstennis? Ikke ta med gange, det kommer i neste spørsmål.

- Dager per uke
- Ingen (gå til spørsmål 21a)
20b) På en vanlig dag hvor du utførte middels anstrengende fysiske aktiviteter, hvor lang tid brukte du da på dette?

- Timer
- Minutter
- Vet ikke/husker ikke

21a) Hvor mange dager i løpet av de siste 7 dager, gikk du minst 10 minutter i strekk for å komme deg fra ett sted til et annet? Dette inkluderer gange på jobb og hjemme, gange til buss, eller gange som du gjør på tur eller som trening i fritiden.

- Dager per uke
- Ingen (gå til spørsmål 22)

21b) På en vanlig dag hvor du gikk for å komme deg fra et sted til et annet, hvor lang tid brukte du da totalt på å gå?

- Timer
- Minutter
- Vet ikke/husker ikke

22) Dette spørsmålet omfatter all tid du tilbringer i ro (sittende) på jobb, hjemme, på kurs, og på fritiden. Det kan være tiden du sitter ved et arbeidsbord, hos venner, mens du leser eller ligger for å se på TV.

I løpet av de siste 7 dager, hvor land tid brukte du vanligvis totalt på å sitte på en vanlig hverdag?

- Timer
- Minutter
- Vet ikke/husker ikke
23) Nedenfor følger en rekke grunner for å drive med fysisk aktivitet. Vennligst sett ett eller flere kryss for den (de) grunn(e) som er viktige for deg.

- Forebygge helseplager
- Holde vekten nede
- For å se veltrent ut
- Øke prestasjonsevnen
- Gjøre fritiden trivelig
- For å ha det gøy
- Føler jeg må

- Komme i bedre form
- Anbefalt av lege, fysioterapeut eller liknende
- Fysisk og psykisk velvære
- For å treffe og omgås andre mennesker
- Oppbygging etter sykdom/skade
- Oppleve spenning/utfordring
- For å få frisk luft

24) Nedenfor følger en rekke grunner for å ikke drive med fysisk aktivitet. Vennligst sett ett eller flere kryss for den (de) grunn(e) som er viktig(e) for deg.

- Har ikke tid
- Har ikke råd
- Transportproblemer
- Negative erfaringer
- Bevegelsesproblemer
- Tror ikke jeg får det til
- Orker ikke
- Redd for å bli skadet (falle, forstue)
- Vil heller bruke tiden min til andre ting
- Andre grunner, hva: _____________________________________________________
De neste spørsmålene handler om dine vaner knyttet til transport og omfatter dine vanlige måter å komme fra et sted til et annet, inkludert hvordan du kommer deg til og fra jobb, butikker, kino, fritidsstasjoner og så videre.

Merk at du skal angi dine transportvaner separat for sommer og vinter.

<table>
<thead>
<tr>
<th>Transport aktiviteter</th>
</tr>
</thead>
<tbody>
<tr>
<td>De neste spørsmålene handler om dine vaner knyttet til transport og omfatter dine vanlige måter å komme fra et sted til et annet, inkludert hvordan du kommer deg til og fra jobb, butikker, kino, fritidsstasjoner og så videre.</td>
</tr>
<tr>
<td>Merk at du skal angi dine transportvaner separat for sommer og vinter.</td>
</tr>
</tbody>
</table>

25a) Hvor mange dager i en vanlig uke reiser du med et motorisert transportmiddel som tog, buss, bil eller trikk?

<table>
<thead>
<tr>
<th>Om sommeren</th>
<th>Om vinteren</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dager per uke</td>
<td>Dager per uke</td>
</tr>
</tbody>
</table>

25b) På en vanlig dag hvor du reiser med motorisert transportmiddel, hvor lang tid bruker du da totalt i transportmiddelet?

<table>
<thead>
<tr>
<th>Om sommeren</th>
<th>Om vinteren</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timer</td>
<td>Timer</td>
</tr>
<tr>
<td>Minutter</td>
<td>Minutter</td>
</tr>
</tbody>
</table>

26a) Hvor mange dager i en vanlig uke sykler du minst 10 minutter i strekk for å komme fra et sted til ett annet?

<table>
<thead>
<tr>
<th>Om sommeren</th>
<th>Om vinteren</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dager per uke</td>
<td>Dager per uke</td>
</tr>
</tbody>
</table>

26b) På en vanlig dag hvor du sykler for å komme deg fra et sted til ett annet, hvor lang tid bruker du da totalt på å sykle?

<table>
<thead>
<tr>
<th>Om sommeren</th>
<th>Om vinteren</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timer</td>
<td>Timer</td>
</tr>
<tr>
<td>Minutter</td>
<td>Minutter</td>
</tr>
</tbody>
</table>
27a) Hvor mange dager i en vanlig uke går du minst 10 minutter i strekk for å komme fra et sted til et annet?

Om sommeren

☐ Dager per uke

Om vinteren

☐ Dager per uke

27b) På en vanlig dag hvor du går for å komme deg fra et sted til et annet, hvor lang tid bruker du da totalt på å gå?

Om sommeren

☐ Timer ☐ Minutter

Om vinteren

☐ Timer ☐ Minutter

28) Dersom du er yrkesaktiv, hvordan kommer du deg vanligvis til og fra arbeid?

☐ Bil/motorsykkel

☐ Offentlig transport (tog, buss, og liknende)

☐ Sykkel

☐ Til fots

☐ Ikke aktuelt

TV, PC og søvnvaner

De neste spørsmålene handler om dine vaner knyttet til bruk av TV og PC utenom jobb. I tillegg vil vi kartlegge dine søvnvaner

29) Utenom jobb: Hvor mange timer ser du vanligvis på TV og sitter med PC på en hverdag? (Sett ett kryss)

☐ Mindre enn 1 time

☐ 1 - 2 timer

☐ 2 - 3 timer

☐ 3 - 4 timer

☐ 4 - 5 timer

☐ Mer enn 5 timer

30) Utenom jobb: Hvor mange timer ser du vanligvis på TV og sitter med PC på en helgedag? (Sett ett kryss)

☐ Mindre enn 1 time

☐ 1 - 2 timer

☐ 2 - 3 timer

☐ 3 - 4 timer

☐ 4 - 5 timer

☐ Mer enn 5 timer
31) Hvor mange timer i døgnet sover du vanligvis på en hverdag?
(Setter ett kryss)
☐ Mindre enn 3 timer    ☐ 8 - 10 timer
☐ 3 - 5 timer          ☐ 10 timer eller mer
☐ 5 - 8 timer

32) Hvor mange timer i døgnet sover du vanligvis på en helgedag eller fridag?
(Setter ett kryss)
☐ Mindre enn 3 timer    ☐ 8 - 10 timer
☐ 3 - 5 timer          ☐ 10 timer eller mer
☐ 5 - 8 timer

Kosthold, røyk og alkohol

I denne delen av spørreskjemaet er det fokus på kosthold og dine røyke- og alkoholvaner. Vi er klar over at kostholdet varierer fra dag til dag. Prøv derfor så godt du klarer å ta ett gjennomsnitt av dine spisevaner og ha det siste året i tankene når du svarer.

33) Har du røukt/røyker du daglig? (setter ett kryss)
☐ Ja, nå ☐ Ja, tidligere ☐ Aldri (Gå videre til spørsmål 36)

34) Hvis du har røukt daglig tidligere, hvor lenge siden er det du sluttet?
☐ ___ år

35) Hvis du røyker daglig nå eller har røykt tidligere:

Hvor mange sigaretter røyker eller røykte du vanligvis daglig?
☐ ___ Antall sigaretter

Hvor gammel var du da du begynte å røyke?
☐ ___ Alder i år

Hvor mange år til sammen har du røykt daglig?
☐ ___ Antall år
36) Bruker du snus? (sett ett kryss)
   - Ja, daglig
   - Av og til
   - Aldri

37) Hvor ofte drikker du alkohol? (Sett ett kryss som stemmer best med dine vaner)
   - Aldri
   - Månedlig eller sjeldnere
   - 2 - 4 ganger pr måned
   - 2 - 3 ganger per uke
   - 4 ganger i uken eller oftere

38) Når du drikker alkohol, hvor mange "drinker" tar du vanligvis?
   En "drink" tilsvarer en ½ liter pils, ett glass vin, ett drammeglass
   (Dersom du ikke drikker alkohol skal du ikke krysse)
   - 1 - 2
   - 3 - 4
   - 5 - 6
   - 7 - 8
   - 9 eller mer

39) Hvor mange enheter med frukt og grønnsaker spiser du i gjennomsnitt hver dag?
   (Med enhet menes for eksempel 1 frukt, 1 glass juice, 2-3 poteter, 1 skål bær, 1 porsjon grønnsaker, 1 porsjon salat)
   - Antall porsjoner frukt
   - Antall porsjoner grønnsaker

40) Hvor ofte pleier du å spise følgende måltider i løpet av en uke?
   (Sett ett kryss for hvert måltid)
<table>
<thead>
<tr>
<th>Aldri/ Sjelden</th>
<th>1 g/uke</th>
<th>2 g/uke</th>
<th>3 g/uke</th>
<th>4 g/uke</th>
<th>5 g/uke</th>
<th>6 g/uke</th>
<th>Hver dag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frokost……...</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Lunsj..........</td>
<td></td>
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<tr>
<td>Middag……...</td>
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</tr>
<tr>
<td>Kveldsmat…</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
41) Hvor ofte spiser du vanligvis disse matvarene? 
(Sett ett kryss per linje)

<table>
<thead>
<tr>
<th>Matvare</th>
<th>0-1 g/mond</th>
<th>2-3 g/mond</th>
<th>1-3 g/uke</th>
<th>4-6 g/uke</th>
<th>1-2 g/dag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poteter (kokte, stekte, potetmos)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Pasta/ris</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Kjøtt (reint kjøtt av storfe, lam, svin, vilt)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Kvernet kjøtt (pølser, hamburger, kjøttdeig, kjøttkaker)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Kylling</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Grønnsaker (ikke poteter)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Frukt og bær</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Mager fisk (torsk, sei, ol)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Fet fisk (laks, ørret, makrell, sild, kveite, uer, ol)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Grovt brød</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Salt snacks (potetgull, saltstenger, ol)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Godteri/sjokolade</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Kaker/kjeks</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
42) Hvor mye drikker du vanligvis av følgende? (Sett ett kryss for hver linje)

<table>
<thead>
<tr>
<th></th>
<th>Sjelden/ aldri</th>
<th>1-3 glass pr mnd</th>
<th>1-3 glass pr uke</th>
<th>4-6 glass pr uke</th>
<th>1-3 glass pr dag</th>
<th>4-6 glass pr dag</th>
<th>&gt;7 glass pr dag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helmelk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lettmelk</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ekstra lett melk</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Skummet melk</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Juice</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vann</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brus med sukker</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brus uten sukker</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaffe</td>
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<td>Te</td>
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<td></td>
</tr>
<tr>
<td>Pils</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brennevin</td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

Holdninger til fysisk aktivitet

I denne siste delen er det fokus på dine holdninger til fysisk aktivitet. Du nærmer deg slutt av skjemaet. Hold ut 😊

43) Tenk deg alle former for fysisk aktivitet. Ta stilling til påstanden: Jeg er sikker på at jeg kan gjennomføre planlagt fysisk aktivitet selv om:

<table>
<thead>
<tr>
<th></th>
<th>Ikke i det hele tatt</th>
<th>Veldig sikker</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 2 3 4 5</td>
<td>6 7</td>
</tr>
<tr>
<td>Jeg er trett</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jeg føler meg nedtrykt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jeg er bekymret</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jeg er sint på grunn av noe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jeg føler meg stresset</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
44) Tenk på alle former for fysisk aktivitet. For hver påstand, angi i hvilken grad du er enig/uenig. (Sett ett kryss for hver påstand)

<table>
<thead>
<tr>
<th>Påstand</th>
<th>Helt enig</th>
<th>Helt uenig</th>
<th>Passer dårlig</th>
<th>Passer bra</th>
</tr>
</thead>
<tbody>
<tr>
<td>Om jeg er regelmessig fysisk aktiv eller ikke er helt opp til meg.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hvis jeg ville, hadde jeg ikke hatt noen problemer med å være regelmessig fysisk aktiv.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jeg ville likt å være regelmessig aktiv, men jeg vet ikke riktig om jeg kan få det til.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jeg har full kontroll over å være regelmessig fysisk aktiv.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Å være regelmessig fysisk aktiv er vanskelig for meg.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

45) I hvilken grad beskriver disse påstandene deg som person?
(Sett ett kryss for hver påstand)

<table>
<thead>
<tr>
<th>Påstand</th>
<th>Aldri</th>
<th>Sjelden</th>
<th>Noen få ganger</th>
<th>Ofte</th>
<th>Veldig ofte</th>
<th>Passer ikke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeg ser på meg selv som en person som er opptatt av fysisk aktivitet.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jeg tenker på meg selv som en person som er opptatt av å holde seg i god fysisk form.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Å være fysisk aktiv er en viktig del av hvem jeg er.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

46) Har familien din (medlemmer i husstanden):
(Sett ett kryss for hver påstand)

<table>
<thead>
<tr>
<th>Påstand</th>
<th>Aldri</th>
<th>Sjelden</th>
<th>Noen få ganger</th>
<th>Ofte</th>
<th>Veldig ofte</th>
<th>Passer ikke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oppmuntring teg til å være fysisk aktiv.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diskutert fysisk aktivitet sammen med deg.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forandret planene sine slik at dere kunne drive fysisk aktivitet sammen.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overtatt oppgaver for deg, slik at du fikk mer tid til å være fysisk aktiv.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sagt at fysisk aktivitet vil være bra for helsen din.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snakket om hvor godt de liker å være fysisk aktive.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
47) Har vennene dine/bekjente/familiemedlemmer utenfor husstanden:
(Sett ett kryss for hver påstand)

<table>
<thead>
<tr>
<th>Foreslått at dere skulle drive fysisk aktivitet sammen</th>
<th>Aldri</th>
<th>Sjelden</th>
<th>Noen få ganger</th>
<th>Ofte</th>
<th>Veldig ofte</th>
<th>Passer ikke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Oppmuntrert deg til å være fysisk aktiv……………..</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Gitt deg hjelsomme påminnelser om fysisk aktivitet som: “Skal du mosjonere i kveld”?……</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Forandret planene sine slik at dere kunne drive fysisk aktivitet sammen……………….</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Sagt at fysisk aktivitet vil være bra for helsen din……………………………………</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Snakket om hvor godt de liker å være fysisk active……………………………………….</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

48) Er det i ditt nærmiljø:
(Sett ett kryss for hver påstand)

| Trygge steder å gå (park/friområde, turvei, fortau) som er tilstrekkelig opplyst…………………. | Helt uenig | Litt uenig | Litt enig | Helt enig |
|                                                                                           | ☐          | ☐           | ☐          | ☐         |
| Mange steder der du kan være fysisk aktiv (utendørs, svømmehall etc.)………………………… | ☐          | ☐           | ☐          | ☐         |
| Flere tilrettelagte tilbud om trening og fysisk aktivitet (som kunne være aktuelle for deg)…………………………………. | ☐          | ☐           | ☐          | ☐         |
| Greit å gå til butikker (10-15 min å gå, fortau langs de fleste veiene)………………………… | ☐          | ☐           | ☐          | ☐         |
| Lett tilgang til gang- eller sykkelveier………………………………………………………….. | ☐          | ☐           | ☐          | ☐         |
| Så mye trafikk i gatene at det er vanskelig eller lite hyggelig å gå……… | ☐          | ☐           | ☐          | ☐         |
| Fotgjengeroverganger og lyssignal som gjør det enklere å krysse veien…………………………… | ☐          | ☐           | ☐          | ☐         |
49) Omtrent hvor lang tid vil det ta deg å gå hjemmefra til:  
(Sett ett kryss for hver linje)

<table>
<thead>
<tr>
<th>Aktivitet</th>
<th>1-5 min</th>
<th>6-10 min</th>
<th>11-20 min</th>
<th>21-30 min</th>
<th>&gt; 30 min</th>
<th>Vet ikke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butikk for dagligvarer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et friområde/park/turnei</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helsestudio/treningscenter/svømmehall/idrettsanlegg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skog/mark/fjell</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

50) I hvilken utstrekning mener du at daglig fysisk aktivitet kan ha gunstig effekt for å forebygge følgende sykdommer: (Sett ett kryss for hver linje)

<table>
<thead>
<tr>
<th>Sykdom</th>
<th>Stor effekt</th>
<th>Liten effekt</th>
<th>Ingen effekt</th>
<th>Vet ikke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hjerte- og karsykdom</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muskel- og skjelettidelser</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes type 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kreft</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Høyt blodtrykk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psykiske lidelser</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overvekt og fedme</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mage-/tarmsykdommer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astma og allergi</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KOLS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Etter at du har fylt ut spørreskjemaet og gått med aktivitetsmåleren i 7 dager, legger du skjemaet og aktivitetsmåleren i den vedlagte konvoluten og returnerer den til oss.

😊 Tusen takk for hjelpen 😊
Appendix III

Part II

Approval from the Regional Committees for Medical Research Ethics

Approval from the Norwegian Social Science Data Services
2010/2008a Fysisk form og effekt av trening hos pasienter operert for lungekreft


Prosjektleder: Stipendiat Elisabeth Edvardsen
Forskningsansvarlig: Oslo universitetssykehus


Data skal innhentes i prosjektet ved undersøkelser, testing og ved bruk av spørreskjemaet "Lungekreftstudien".

En belastning for pasientene kan ligge i å måtte gjennomgå prøve for å finne maks O2-opptak. Ellers vurderes deltakelse i prosjektet å ha ulemper i forhold til nytten for den enkelte og for fordelen med å få ny kunnskap om rehabilitering av denne pasientgruppen.

Komiteen har vurdert prosjektet. Det kan være et problem at kontrollgruppen ikke får den intervensionen som en mener det er sannsynlig kan ha en positiv effekt. Men i og med at det ikke finnes noen etablert kunnskap, og at formålet med prosjektet er å finne ut om det har noen effekt, må det være akseptabelt å ha en kontrollgruppe som ikke får det samme tilbudet. Det blir også greit gjort rede for fordelingen til de to gruppen i informasjonsskrivet.

Vedtak:
Komiteen godkjenner at prosjektet gjennomføres i samsvar med det som framgår av søknaden.

Dersom det skal gjøres endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende endringsmelding til REK.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter».
innenfor helse- og omsorgssektoren». Personidentifiserbare data slettes straks det ikke lenger er behov for dem og senest ved prosjektets avslutning.


Vennligst oppgi vårt saksnummer/referansenummer i korrespondansen.

Med vennlig hilsen

Gunnar Nicolaysen (sign)
Professor
Leder

Jørgen Hardang
Komitésekretær

Kopi: o.h.skjonsberg@medisin.uio.no, godkjenning@rikshospitalet.no
PERSONVERNOMBUDETS UTTELELSE

Til: Ole Henning Skjønsberg, prosjektleder
Kopi: Elisabeth Edvardsen, leder prosjektmedarbeider
Fra: Personvernombudet ved Oslo universitetssykehus
Saksbehandler: Helge Grimnes
Dato: 04.10.2010
Offendighet: Ikke unntatt offentlighet
Sak: Personvernombudets uttalelse til innsamling og behandling av personopplysninger i forskningsstudie

Saksnummer/Personenummer: 1538

Personvernombudets uttalelse til innsamling og behandling av personopplysninger for forskning i prosjektet "Kardiorespiratorisk form og effekt av rehabilitering etter operasjon for lungekreft"

Viser til innsendt melding om behandling av personopplysninger / helseopplysninger. Det følgende er et formelt svar på meldingen. Forutsetningene nedenfor må være oppfylt før rekruttering av pasienter til studien kan starte.

Personvernombudet har vurdert det til at den planlagte databehandlingen av personopplysninger / helseopplysninger tilfredsstiller de krav som stilles i helse- og personvernlovgivningen.

Personvernombudet har ingen innvendinger til at den planlagte databehandlingen av personopplysninger / helseopplysninger kan igangsettes under forutsetning av følgende:

1. Behandling av personopplysningene / helseopplysninger i studien skjer i samsvar med og innenfor det formål som er oppgitt i meldingen.
2. Studien må vurderes og godkjennes av Regional komité for medisinsk og helsefaglig forskningsetikk (REK), og eventuelle merknader må følges. Kopi av anbefaling fra personvernombudet kan vedlegges søknaden til REK.
6. Dersom formålet, utvalget av inkluderte eller databehandlingen endres må personvernombudet gis forhåndsinformasjon om dette.
Studien er registrert i sykehusets offentlig tilgjengelig database over forsknings- og kvalitetsstudier.

Lykke til med studien!

Med vennlig hilsen
for Personvernombudet

Helge Ørénnes
Personvernrådgiver
Kompetansesenter for personvern og sikkerhet
Oslo universitetssykehus HF

Epost: personvern@rikshospitalet.no
Web: www.uus.no/personvern
Appendix 4

Part II

Consent forms and Study information
Forespørsel om deltakelse i forskningsprosjektet

Kardiorespiratorisk form og effekt av rehabilitering etter operasjon for lungekreft

Bakgrunn og hensikt
Dette er et spørsmål til deg om å delta i en forskningsstudie som har til hensikt å undersøke forandring i lungefunksjon og fysisk kapasitet etter operasjon for lungekreft, samt studere effekt av trening og rehabilitering etter operasjon.


Hva innebærer studien?


Hvis man i løpet av studien skulle avdekke uforutsette medisinske funn, vil legen din bli informert umiddelbart, og adekvat behandling vil straks bli igangsatt.

**Mulige fordeler og ulemper**


**Hva skjer med informasjonen om deg**

**Frivillig deltagelse**


---

**Samtykke for deltagelse i studien**

Jeg er villig til å delta i studien

________________________________________________________________________________________

Signert av prosjektdeleker

Dato

---

**Bekreftelse på at informasjon er gitt deltakeren i studien**

Jeg bekrefter å ha gitt informasjon om studien

________________________________________________________________________________________

Prosjektleder

Dato
Forespørsel om deltakelse i forskningsprosjektet

Kardiorespiratorisk form før og etter operasjon for lungekreft

Bakgrunn og hensikt
Dette er et spørsmål til deg om å delta i en forskningsstudie som har til hensikt å undersøke forandringer i lungefunksjon, fysisk form og aktivitetsnivå etter operasjon for lungekreft.


Hva innebærer studien?

Mulige fordeler og ulemper
Fordelen ved deltakelse i studien er at helsetilstanden din vil bli grundig fulgt opp fra før til 6 mnd etter operasjon. Du vil få god innsikt i egen helsesituasjon gjennom behandlingen. Hvis man i løpet av studien skulle avdekke uforutsette medisinske funn, vil legen din bli informert umiddelbart, og adekvat behandling vil straks bli igangsatt. Erfaringer fra studien vil senere kunne hjelpe andre i samme situasjon.

Hva skjer med informasjonen om deg

Frivillig deltagelse

Studien ledes av Elisabeth Edvardsen i samarbeid med professor Ole Henning Skjønsberg og Seksjonsoverlege Fredrik Borchsenius på Lungemedisinsk avdeling.
Dersom du har spørsmål til studien eller senere ønsker å trekke deg, kan du kontakte prosjektleder Elisabeth Edvardsen på tlf 452 66 452 eller 922 09 595.

Samtykke for deltagelse i studien

Jeg er villig til å delta i studien

---------------------------------------------------------------------------
Signert av prosjektleder

Dato

Bekreftelse på at informasjon er gitt deltakeren i studien

Jeg bekrefter å ha gitt informasjon om studien

---------------------------------------------------------------------------
Prosjektleder

Dato
Lunefunksjon, fysisk form og effekt av rehabilitering etter operasjon for lungekreft
SKAL DU OPERERES FOR LUNGEKREFT?
Da ønsker vi å invitere deg til deltakelse i et forskningsprosjekt

Hvordan endres lungefunksjonen og den fysiske formen etter operasjon for lungekreft?

Er trening etter operasjon gunstig for opererte lungekreftpasienter, og kan fysisk aktivitet påvirke livskvaliteten under den videre behandlingen?

Dette er noen av de spørsmålene vi ønsker å få svar på ved å invitere deg til å delta i dette forsknings-prosjektet.

Bakgrunn
Vi vet fra andre undersøkelser at fysisk aktivitet og trening øker hjertets pumpekapasitet og bedrer oksygenopptaket i muskulaturen. Dette fører til at man blir mindre andpusten under fysiske anstrengelser, noe som er gunstig for personer med redusert lungekapasitet. I tillegg gir fysisk aktivitet bedre søvnkvalitet, styrker kroppens immunforsvar, gir gunstig vektregulering og reduserer angst og depresjon. Fysisk aktivitet kan dermed gi økt livskvalitet.

Målsetning
Målsetning med studien er å undersøke hvor mye lungefunksjonen og kondisjonen endres etter at man har fjernet deler av- eller en hel lunge, samt studere effekt av trening hos lungekreftpasienter. Dette har ikke blitt studert på denne pasientgruppen tidligere.
Vi planlegger å inkludere ca 100 lungekreftpasienter under 80 år som opereres ved Oslo universitetssykehus og Akershus universitetssykehus. Ca 50 pasienter trekkes til deltakelse i treningsgruppen og ca 50 pasienter til kontrollgruppen.

Alle deltakere skal gjennomføre en kartlegging av lungefunksjonen og den fysiske formen før operasjon, fire uker etter operasjon og etter 6 mnd. I tillegg skal ulike spørreskjema bevares i løpet av perioden.

Ca fire uker etter operasjonen vil du bli trukket enten til treningsgruppe eller kontrollgruppe.

Kontrollgruppen vil følge det vanlige behandlingsopplegget som gir for lungekreftpasienter i dag.

Deltakere i treningsgruppen skal trene totalt tre ganger i uken og vil bestå av individuell veiledning av fysioterapeut og egen personlig trener i tillegg til grupptrening sammen med andre pasienter.

Treningen vil bestå av øvings-, kondisjon-, balance-, og bevegelighetstrening og være tilpasset både din sykdomssituasjon og dagsform. Alle fysiotrener og personlige trener i prosjektet har god utdannelse innen sitt fagfelt og kan derfor gi deg gode råd i forhold til smerte, forebygging av skader, hjelp til å redusere engstelse, samt oppmuntre deg til å være så aktiv som mulig.

Kontakt oss!
Hvis du har spørsmål vedrørende studien kan du kontakte prosjektleder Elisabeth Edvardsen på e-post: falc@nih.no eller ringe FALC telefonen på nummer: 452 66 452
MÅLING AV KROPPSSAMMENSETNING
DXA - UNDERSØKELSE

I forbindelse med din deltagelse i lungekreftstudien vil du måle kroppssammensetningen din – såkalt DXA. DXA er en spesiell form for røntgenundersøkelse som gir et mål på kroppens sammensetning av muskulatur, ben og fettvev.

Undersøkelsen tar ca 20-30 minutter, er helt smertefri og innebærer liten strålebelastning. Du må ligge helt i ro på en undersøkelsesbenk mens apparatet beveger seg med en summende lyd over deg. Fordi røntgenstrålene bremses av metall må du ta av deg alt av metall, for eksempel bukse med glidelås, beltespenne, smykker og lignende.

DXA-undersøkelsen foregår på Ullevål universitetssykehus ved Ortopedisk senter. En medhjelper i studien vil følge deg og være med deg under hele undersøkelsen.