Nutrition and energy expenditure in women with chronic obstructive pulmonary disease

Nighat Farooqi
One of my ambitions is to dissuade health professionals from saying: "There's nothing more that can be done." Apart from the devastating effect it has on the people, it is simply not true. What is meant is that there is no cure, no magic, but there is always something that can be done.

Trevor Clay

Dedicated to my dear family
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Abstract

Background/Aim: Chronic Obstructive Pulmonary Disease (COPD) is a respiratory disease with manifestations in many organ systems including weight loss and nutritional problems. It is a major cause of morbidity and mortality for which low body-weight (BW), low fat-free mass (FFM) and low body mass index (BMI) are important risk factors. Individually adapted nutritional support to COPD patients losing weight is important. In order to provide successful nutritional intervention, there is a need to have validated and easy to use methods to estimate total daily energy expenditure (TEE), energy intake (EI), and energy requirement. Studies considering the evaluation of methods to estimate TEE, EI and energy expenditure are scarce in COPD patients. Furthermore, the frequency and distribution of underweight in COPD patients with different severity, and gender differences, have not been clearly addressed in population-based studies. The overall objective of this thesis was therefore to validate and increase the knowledge of methods for assessment of TEE, EI, and energy requirement in COPD. We also investigated the relationship of BMI with clinical characteristics of COPD in a population-based study. Due to the substantial and increasing morbidity in women with COPD, special attention was given to this group.

Methods: Resting metabolic rate (RMR) was measured by indirect calorimetry (IC). TEE was measured by criterion method, doubly labeled water (DLW) (Paper I-III) during a 14-day period. TEE was simultaneously assessed by SenseWear Armband, software version 5.1 and 6.1 (SWA5 respectively SWA6), and ActiHeart (paper I). EI was assessed by diet history interview and 7-day food diary (paper II), and energy requirement was predicted using pedometer-determined physical activity level (paper III). Energy requirement data was also acquired from studies concerning TEE measured by DLW in patients with COPD (paper IV). BMI and other characteristics in subjects with COPD were compared with non-COPD subjects in a population-based study, Obstructive Lung disease in Norrbotten study (OLIN) (paper V).

Results: There was a large variation in RMR and TEE measured by DLW in this group of women with COPD. The results of energy expenditure study showed that the SWA5 assessed TEE with good accuracy over a 14-day period in free-living women with COPD. However, the SWA6 and ActiHeart methods tend to underestimate TEE. A higher proportion of women were within ± 5% of the TEE individually measured with the DLW method using SWA5 than SWA6 and AH (63%, 47%, 37% respectively). The agreement between the TEE measured by DLW and SWA5 was strong, and with SWA6 and ActiHeart it was lesser. Bland-Altman plots revealed no systematic bias for TEE. The reported EI was underestimated by 28% respectively 20 % when assessed by diet, and the 7-day food diary compared with the criterion method, DLW. More women were identified as valid-reporters based on their 7-day food diaries than on their diet histories (63% vs 32%). The accuracy of reported EI was only related to BMI. The agreement between the DLW and the EI methods was weak. The Bland-Altman plots revealed a slight systematic bias for both methods.
The energy requirement predicted by pedometer-determined PAL multiplied by six different RMR equations was within a reasonable accuracy (±10%) of the measured TEE for all equations except one. The agreement between the DLW and four of six predicted TEE methods was strong. The Bland–Altman plots revealed no systematic bias for predicted energy requirement except for one. Estimated PAL from the pedometer was lower by 14% than the measured criterion PAL.

The energy requirement calculation based on available TEE data measured by DLW varied by BW and FFM. Compared to men, women had a lower RMR and TEE/kg BW/day, and higher RMR and TEE/kg FFM/day. The correlates of RMR/kg BW were gender and forced expiratory volume in 1st second (FEV₁) % of predicted value, of TEE/kg BW the correlates were age and gender, and of TEE/kg FFM were age and FEV₁ % predicted. BMI decreased significantly with increase in disease severity and correlated significantly to forced expiratory volume in 1st second % predicted.

In the population-based study (OLIN), subjects with COPD had lower BMI and a higher prevalence of under-weight than in non-COPD, and its sub-groups namely, normal lung function and restrictive spirometry pattern subjects. There was an independent association between COPD and low BMI. Fewer COPD subjects were obese than in the non-COPD, normal lung function and restrictive spirometry pattern groups. Among the subjects with COPD, women had a lower mean BMI and a higher proportion were under-weight than men. In COPD women with under-weight, FEV₁ % predicted values increased with an increase in BMI.

**Conclusion:** Compared with the gold standard DLW method, the total daily energy expenditure can be assessed reliably by SenseWear Armband 5 in women with COPD, while other devices underestimated TEE. The energy intake was underestimated by diet history and 7-day food diary methods, and energy requirement was predicted with reasonable accuracy using pedometer-determined PAL and common RMR equations, compared with DLW. Furthermore, the energy requirement was determined per kg BW/day and per kg FFM/day, using DLW based TEE data in patients with COPD. In the population-based study (OLIN), subjects with COPD had lower BMI and higher prevalence of under-weight than subjects without COPD. There was a gender difference, which was particularly significant in COPD, for women to have lower mean BMI and a higher prevalence of under-weight.

The present findings indicate that low BMI is common in COPD and needs to be intervened. For a successful nutritional treatment, it is imperative to assess the patient's energy expenditure, intake, and the requirement objectively, considering the burden of COPD, especially in women.

**Key words:** Energy expenditure and COPD; Energy intake and COPD; Energy requirement and COPD; Women with COPD; DLW and COPD; SenseWear Armband and COPD; ActiHeart and COPD; Pedometer-determined PAL; BMI and COPD.
Svensk Sammanfattning

(Summary in Swedish)


Metoder: Viloenergiförbrukning mättes med indirekt kalorimeter hos kvinnor med KOL. Den totala energiförbrukningen mättes hos dessa kvinnor med dubbelmärktvatten metoden (DLW) (Arbete 1-3) under en 14-dagars period. Samtidigt bedömdes energiförbrukningen med två aktivitetsmätare, SenseWear Armband, mjukvaruversion 5.1 och 6.1 (SWA5 respektive SWA6), och ActiHeart (arbete 1). Energiintaget bedömdes med kostanamnes och 7-dagars matdagbok (arbete 2); energibehovet beräknades med olika viloenergiförbruknings formler och fysisk aktivitetsnivå uppskattad med en steigräknare (arbete 3). En sammanställning och en analys genomfördes av energibehovet baserad på data från flera studier som har mätt TEE med DLW hos KOL patienter (Arbete 4). BMI och kliniska egenskaper jämfördes mellan personer med och utan KOL i ett stort populationsbaserat material från Obstruktiv Lungenjukdom i Norrbotten (OLIN) studien (Arbete 5).

Resultat: Det fanns en stor variation i viloenergiförbrukningen och energiförbrukning mätt med DLW hos kvinnor med KOL. Energiförbrukningen mätt med aktivitetsmätare SWA5 visade hög tillförlitlighet både på grupp- och individnivå, medan SWA6 och ActiHeart metoderna underskattade energiförbrukningen. Energiintaget bedömd med kostanamnes och 7-dagars matdagbok visade en underskattning med 28% respektive 20% jämfört med DLW metoden. Det rapporterade energiintaget stämde för flertalet kvinnor bättre mot DLW metoden när energiintaget bedömdes med 7-dagars matdagbok jämfört med kostanamnes (63 % mot 32%). Det beräknade energibehovet från steigräknare och från fem av sex olika RMR ekvationer låg inom en rimlig marginal (± 10 %) jämfört med den uppmätta energiförbrukningen med DLW. Beräkning av energibehov baserat på tillgängliga data om energiförbrukning mätt med DLW varierade utifrån kroppsvikt och fettsjukdoma hos patienter med KOL. Kvinnor hade en lägre viloenergiförbrukning och energiförbrukning per kg kroppsvikt och dag, och högre daglig viloenergiförbrukning och energiförbrukning per kg fettsjukdom och dag jämfört med män.
I den populationsbaserade studien hade personer med KOL signifikant lägre BMI och högre prevalens av undervikt än personer utan KOL. Det fanns ett oberoende samband mellan KOL och lågt BMI. Färre personer med KOL var överviktiga än personer som inte hade KOL. Kvinnor med KOL hade både lägre BMI och högre andel med undervikt än män med KOL.

**Slutsats:** SenseWear Armband med programvaran 5.1 visar sig kunna beräkna den totala energiförbrukningen på ett tillförlitligt sätt hos kvinnor med KOL. Energiintaget beräknat utifrån kostanamnes och 7-dagars matdagbok underskattades. Energibehovet kan beräknas med en rimlig precision med hjälp av stegräknare och viloenergiförbrukningsformler hos dessa kvinnor. De sammanställda data om energiförbrukning mätt med DLW kan användas för att beräkna energibehov per kg- kroppsvikt och fettfri massa hos patienter med KOL i kliniskt syfte. I det populationsbaserade materialet från OLIN-studien noterades ett lägre BMI och högre prevalens av undervikt hos personer med KOL, och detsamma resultat förekom hos kvinnor med KOL jämfört med män med KOL.
Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AEE</td>
<td>Activity energy expenditure</td>
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<tr>
<td>AH</td>
<td>ActiHeart</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<td>BW</td>
<td>Bodyweight</td>
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<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
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<td>CI</td>
<td>Confidence interval</td>
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<td>DH</td>
<td>Diet history interview</td>
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<td>DIT</td>
<td>Diet induced thermogenesis</td>
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<td>DLW</td>
<td>Doubly labeled water</td>
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<td>DXA</td>
<td>Dual-energy X-ray absorptiometry</td>
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<tr>
<td>EI</td>
<td>Energy intake</td>
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<tr>
<td>FEV₁</td>
<td>Forced expiratory volume in 1st second</td>
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<tr>
<td>FEV₁%</td>
<td>Forced expiratory volume in 1st second in per cent of predicted value</td>
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<tr>
<td>FD</td>
<td>Food diary</td>
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<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
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<td>FFM</td>
<td>Fat-free mass</td>
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<tr>
<td>FFMI</td>
<td>Fat-free mass index</td>
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<td>GOLD</td>
<td>Global Initiative for Chronic Obstructive Lung Disease</td>
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<td>HRQoL</td>
<td>Health-related quality of life</td>
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<tr>
<td>ICC</td>
<td>Intraclass correlation coefficient</td>
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<tr>
<td>kJ</td>
<td>Kilojoule</td>
</tr>
<tr>
<td>NLF</td>
<td>Normal lung function</td>
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<tr>
<td>OLIN</td>
<td>Obstructive Lung Disease in Northern Sweden Studies</td>
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<td>PAL</td>
<td>Physical activity level</td>
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<td>RMR</td>
<td>Resting metabolic rate</td>
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<td>RSP</td>
<td>Restrictive Spirometry Pattern</td>
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<td>SD</td>
<td>Standard deviation</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>SVC</td>
<td>Slow vital capacity</td>
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<td>SWA</td>
<td>SenseWear Armband</td>
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<td>TEE</td>
<td>Total daily energy expenditure</td>
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<td>WHO</td>
<td>World Health Organization</td>
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The present thesis is based on the following papers, which will be referred by their Roman numerals:


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Background

Chronic Obstructive Pulmonary Disease (COPD), is a respiratory disease with manifestations in many organ systems and often includes weight loss with nutrition problems. It is a major cause of morbidity and mortality and represents a substantial economic and social burden throughout the world (1,2).

Definition

According to Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD is defined as “a common preventable and treatable disease, that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.” (3).

COPD is a slowly progressive disease involving the airways or pulmonary parenchyma or both that results in airflow obstruction (4). COPD is characterized by respiratory symptoms — dyspnea, cough, and sputum production, airflow limitation, and chronic inflammation of the lung (3,4). COPD patients to varying degree may present chronic bronchitis, bronchiolitis, and emphysema (5). Damage to the airways eventually interferes with the exchange of oxygen and carbon dioxide in the lungs (5).

Diagnosis

Spirometry is essential for the diagnosis of COPD and provides a useful description of the severity of pathological changes in this disease (3). GOLD criteria for COPD diagnosis is a post-bronchodilator spirometry of forced expiratory volume in 1st s/forced vital capacity (FEV1/FVC) < 0.70 (3). Further, COPD is classified by disease severity (3) (Table 1). The impact of COPD depends both on the degree of symptoms and severity of the airflow limitation (3).
Table 1. GOLD classification of COPD severity based on post-bronchodilator spirometry in patients with FEV₁/FVC < 0.70 (3).

<table>
<thead>
<tr>
<th>GOLD 1</th>
<th>Mild</th>
<th>FEV₁ ≥ 80% of predicted value</th>
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<tr>
<td>GOLD 2</td>
<td>Moderate</td>
<td>50% ≤ FEV₁ &lt; 80% of predicted value</td>
</tr>
<tr>
<td>GOLD 3</td>
<td>Severe</td>
<td>30% ≤ FEV₁ &lt; 50% of predicted value</td>
</tr>
<tr>
<td>GOLD 4</td>
<td>Very Severe</td>
<td>FEV₁ &lt; 30% of predicted value</td>
</tr>
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FEV₁, Forced expiratory volume in one second; FEV, Forced vital capacity.

Pathology

In COPD, the pathological changes are characterized by chronic inflammation throughout the central and peripheral airways, lung parenchyma, and pulmonary vasculature (6). Macrophages, T lymphocytes, and neutrophils are often increased in various parts of lungs. Goblet cells and mucus producing glands are increased in the bronchi. The small airways are affected by bronchiolitis and the alveoli by the destructive process referred to as emphysema. Besides inflammation, several other processes that are thought to be important in the pathogenesis of COPD, including an imbalance of proteinases and anti-proteinases in the lungs, oxidative stress, accelerated aging of tissue and remodeling. The most important cause of the changes in the lungs is the exposure to inhaled harmful particles and gases, predominantly from tobacco smoking.

Systemic effects from the COPD pathology affects the cardiovascular system, muscles, and other organs. The natural history of COPD is often characterized by symptoms such as cough, phlegm, and effort dyspnea (7). Dyspnea or breathlessness is the most significant symptom in COPD patients and is a common reason for seeking medical help.
Epidemiology

Prevalence

Different population survey studies across Europe and USA show different prevalence (3,8). In Sweden, it is estimated that 500 000 – 700 000 people are diagnosed with COPD (9). In northern Sweden, the overall prevalence of COPD in ages > 45 years was 8 % according to British Thoracic Society (BTS) criteria and 14 % according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (10). In Spain the prevalence was 9 % in 40-69 years aged men and women, and in the USA, during 2000, an estimated 10 million adults reported physician-diagnosed COPD (8). Further increases in its prevalence and mortality are expected in the coming decades due to the preceding tobacco smoking history despite advances in its management (1).

Morbidity

Patients with COPD have a substantial morbidity that is often being underestimated by health-care providers and also by the patients (1). The limited data that are available indicate that the morbidity due to COPD increases with age (11). This disease accounts for many visits to physicians, emergency departments, and hospitalizations (1,11).

Mortality

According to World Health Organization, more than 3 million people died of COPD in 2012 and it is estimated to be the third leading cause of mortality globally by 2030 (12). Currently, COPD is the fourth leading cause of death in the world (13). In Sweden, 2575 persons died of COPD in 2013 according to the national death register (ICD-10 code J44) (14).

Burden of COPD

Besides COPD represents a substantial economic and social burden throughout the world (1,2,15), it is a costly disease with both direct and indirect costs (16). The overall annual cost excluding mortality and rehabilitation for COPD in Europe in 2001 was estimated to be € 38.7 billion (€ 4.7 billion for ambulatory care; € 2.7 billion for drugs; € 2.9 billion for inpatient care and € 28.4 billion for lost work days). The total cost (direct and indirect) in 2010 for COPD in Sweden was estimated at € 1.5 billion (17). The economic burden of COPD is likely to be underestimated since, for example, the economic value of the care provided by family members is not
generally acknowledged (8). Long-term home care provided by relatives for patients with severe COPD frequently has a negative effect on professional careers, both for the patients and for the other family members.

**Gender perspective**

Traditionally, COPD has been regarded as a disease of males (18). However, data from developed countries have shown an almost equal prevalence of COPD in women and men (1). In 2000 the absolute number of COPD deaths in females in the USA overtook that of males (19). In Sweden, the prevalence of COPD has increased more among women than among men, likely as a result of long-term smoking (20), and this disease has emerged as an important women’s health issue.

The impact of this disease in women has been underresearched, but the evidence that does exist reveals potentially substantial gender differences in the susceptibility to, severity of, and response to management of COPD (21). Malnutrition, prevalence of symptoms, susceptibility to smoking, frequency of exacerbations, impairment of quality of life, hyper-responsiveness of airways, triggering stimuli, response to treatment and management, and depression are more often seen in females with COPD (21-27). The rate of increase in hospitalizations and deaths from COPD are highest in women, and they are more likely to develop COPD at an earlier age and to have a more severe expression of the disease than men (23,24). There are reports which suggest that women experience more severe dyspnea than men despite the similar FEV\(_1\) or significantly fewer pack-years of smoking (24,25).

Besides the biological gender differences, a bias towards a COPD diagnosis in men has been suggested (24,27). It has been reported that women are less likely to receive spirometry tests than men in the primary health care (24). These reports imply that women may less likely be diagnosed and treated for their COPD.

**Risk factors**

The major risk factor for COPD worldwide is tobacco smoking (6,28). In Sweden, in a populations-based study (OLIN study), Lundbäck et al. have shown that the two dominating risk factors for COPD were increasing age and smoking (9).

It is helpful, conceptually, to think of a person’s exposures in terms of the total burden of inhaled particles. Each type of particle, depending on its size
and composition, may contribute a different weight to the risk and the total risk will depend on the integral of the inhaled exposures. For example, tobacco smoke (active and passive tobacco smoke), outdoor and indoor air pollution, and occupational exposures probably act additively to increase a person’s risk of developing COPD (6). The age at starting smoking, total pack-years smoked, and current smoking status are all predictive of COPD mortality (8). Data from the US NHANES III survey indicate that occupation can be an important risk factor for COPD. The fraction of COPD attributable to work was estimated as 19.2% overall and 31.1% in never-smokers (29). Occupational exposures include organic and inorganic dust and chemical agents and fumes (3).

Socioeconomic status has been shown to be inversely related to the development of COPD (30). Whether the effect is due to exposures to indoor and outdoor air pollutants, crowding, poor nutrition, or other factors related to low socioeconomic status, is not clear (3). In developing countries, indoor air pollution, due to the use of biomass fuels for heating and cooking, may pose a significant particulate burden and contribute to COPD, especially in females (6).

The genetic risk factor that is best documented is a severe hereditary deficiency of α1-antitrypsin, a major circulating inhibitor of serine proteases (31).

**Systemic effects of COPD**

Previously COPD was often looked at as solely a lung disease whereas it is now often associated with significant extrapulmonary abnormalities, the so-called systemic effects of COPD (32). These systemic effects involve the lungs and organs outside the lungs. Examples of extra pulmonary effects are: decreased Health-related quality of life (HRQoL), systemic inflammation, nutritional abnormalities and weight loss, skeletal muscle dysfunction and exercise limitation, osteoporosis, decreased cognitive function, and cardiovascular system abnormalities. Further, these components are interdependent in a closely linked 'vicious cycle.' Accordingly, optimal therapies should, therefore, aim to address more than one of these components to break such a cycle. This needs to be considered not only in the development of future treatments but also in the current clinical management of patients with COPD. By developing a better understanding of how different therapies impact upon the 'vicious cycle' of COPD, treatment regimens can be optimized to provide the greatest benefits to patients.
**Health related quality of life**

Health-related quality of life is impaired in patients with COPD and is an independent predictor of hospitalizations and mortality (33). Women with COPD seem to have a greater HRQoL impairment (33,34). Worsening of HRQoL also appears to be related to decreasing FEV₁, frequent exacerbations, dyspnea, anxiety, depression, body-weight, and a low level of physical activity (34).

**Anxiety and depression**

Anxiety is more prevalent in patients with COPD, who seem to report symptoms of anxiety twice as often as healthy controls (34). Anxiety symptoms comprise of panic disorders, panic attack, general anxiety disorder, and posttraumatic stress disorder in COPD population. The prevalence of lifetime anxiety disorders in patients with COPD ranged from 10% to 96% (34,35). The prevalence of depression in patients with COPD has been indicated to be in the range of 16% to 88% (34,35). Having depression in this group of patients seems to have an influence on hospitalizations, exacerbations, and eventually raised rates of mortality. Depression has been shown to be related to persistent smoking, social withdrawal, lower medical compliance, and impaired health-related quality of life (34). The wide range of prevalence rates could be attributed to several factors: the demographics of the samples, the different instruments used to measure symptoms of anxiety, and depression versus depressive disorders as identified by clinical interviews, and the variation in the cutoff scores of the instruments (35).

Anxiety and depression are among the leading comorbidities in COPD, and the symptoms of these are often overlapping (34). The proportion of patients with COPD with both anxiety and depression has been reported in the range 22% to 48%. The risk of increased anxiety and depression have been related with female gender, younger age, smokers, living alone, body mass index (BMI), dyspnea, having a recent exacerbation, and lower FEV₁ (34,36).

**Physical activity limitation**

Patients with COPD are often considerably less physically active than healthy subjects of the same gender and age, and the low levels of physical activity are associated with poor prognosis (37) and has been suggested as a strong predictor of death in COPD (38). This group of patients spends significantly less time in walking than sedentary healthy elderly subjects, and the pace of walking is significantly slower than healthy subjects (39). In a recent review, it has been reported that the patients with COPD walked on average 2237
steps/day, which was the lowest after disabled older adults (40). Physical activity has been associated with dyspnea, previous exacerbations, hyperinflation, gas exchange, exercise capacity, systemic inflammation, quality of life and self-efficacy (37).

**Skeletal muscle dysfunction**

In COPD the function of skeletal muscles especially the muscles involved in ambulation is impaired, and this dysfunction contributes to exercise intolerance (41). This impairment of muscles seems to be multifactorial. A considerable decrease in strength and endurance may occur as the patients with COPD appear to have decreased muscle capillary density, ambulatory muscle atrophy, and a shift in muscle fiber type from type I and IIA to Ib. Malnutrition may be another contributing factor due to inability to synthesize muscle protein. Other possible contributing factors are exposure to corticosteroids, systemic inflammation, and low levels of anabolic hormones, hypoxia, oxidative stress, heart disease, and cigarette smoking.

**Nutritional abnormalities**

It has been recognized that a gradual and significant weight loss occurs in a substantial number of patients with COPD during the natural course of their illness (42,43). The prevalence of weight loss in patients with COPD has been shown to be 25% - 50% (44). Females with COPD seem to have a higher prevalence of low BMI as well as low fat-free mass index (FFMI) than male COPD patients (44). The main cause of weight loss is the loss of skeletal muscle mass (32).

Some studies have shown that low body-weight or loss of weight in COPD patients is related to reduced performance as well as increased morbidity and mortality (45,47), irrespective of the severity of the respiratory obstruction (47). Furthermore, reduced muscle strength, loss of body mass or subcutaneous fat or protein have been documented in malnourished COPD patients (48,49). The median survival time was reduced by nearly half in lean patients with COPD, from just under 4 years to just over 2 years, irrespective of COPD severity (50). Low body-weight is even associated with osteoporosis (51).

In recent years more focus has been laid on body composition which can be altered in COPD (32). Studies have shown that fat-free mass (FFM) is an independent predictor of mortality (50,52). Problems such as dyspnea, anorexia, depression, anxiety, and fear of gaining weight seem to be common in patients with severe COPD and are related to smoking habits and gender
(53). This affects energy intake (EI) and FFMI negatively (53). Research data suggest that the development of dyspnea is related to nutritional status (54,55). Slimming and fear of gaining weight are also common among women with COPD (53). Women often seem to have a different body image compared with men and use tobacco smoking as a tool to control their body-weight (56,57).

BMI has been independently shown to be a strong predictor of overall mortality at levels below 22.5 kg/m², and above 25 kg/m² (58). Increased mortality below BMI 22.5 kg/m² has been attributed to mainly smoking-related diseases (58). New evidence is emerging regarding the association between low BMI and decreased pulmonary function (59,60). Low BMI is not only suggested to be a systemic consequence of COPD but also an important risk factor for the development of COPD (59). COPD patients with low BMI have a greater risk of acute exacerbations (61) and a higher mortality (62). BMI has been suggested as one of the four parameters suitable for a grading system for risk of mortality in COPD (BODE index) (63).

Different factors and mechanisms may be involved in weight loss and increased metabolic rate. Involuntary loss of weight could be a result of an inadequate dietary intake combined with increased total energy expenditure (TEE) (43). The energy requirement also appears to be increased in COPD patients (64), and this increase has been shown to be strongly associated with a higher rate of breathing at rest and during activity (65,66). Other possible mechanisms that may contribute to the increase in metabolic rate in patients with COPD are the effect of drugs such as β2-agonists, systemic inflammation, and tissue hypoxia (32).

**Osteoporosis**

Osteoporosis is a major comorbidity in COPD (3), and the prevalence is assumed to be higher by two- to five-fold than in matched subjects without airflow obstruction (67). Osteoporosis is more often associated with the decreased body mass index (BMI), low FFM, vitamin D deficiency, disease severity, use of corticosteroids, and sedentary lifestyle (3,67). Poor health status and prognosis are also associated with osteoporosis (3).

**Management of COPD**

The objectives of treatment for COPD include slowing the accelerated decline in lung function, prevent and treat exacerbations, reduce hospitalizations
and mortality, relieving symptoms, such as shortness of breath and cough, and improving exercise tolerance and the quality of life (1,4,6).

**Smoking cessation**

Smoking cessation is the most effective and cost effective intervention in most people to reduce the risk of developing COPD and stop its progression (3). If persons with COPD continue to smoke tobacco their pulmonary function will decline more rapidly than if they quit (68). Most experts advocate early detection of COPD and active intervention to stop smoking. Smoking cessation has been shown to halt the accelerated loss of lung function associated with COPD (69). It also stops the loss of lung function in younger patients with relatively mild disease. However, any COPD patient can benefit from smoking cessation, no matter how advanced the disease.

Reducing the risk from indoor and outdoor air pollution is feasible and requires a combination of public policy and protective steps taken by individual patients (3). Efforts to reduce smoking through public health initiatives should also focus on passive smoking to minimize risks for non-smokers.

**Medication**

The pulmonary component in COPD is characterized by airflow limitation that is not fully reversible and is usually progressive (6). To date, none of the existing medications has been shown to significantly modify the long-term decline in lung function (6,70). Appropriate medications can reduce symptoms of COPD, particularly shortness of breath, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance (70). Treatment with medications needs to be patient specific - the severity of symptoms, risk of exacerbations, comorbidities, drug availability, and the patient’s response should be considered.

Currently, available medications that are helpful in treating COPD include bronchodilators and corticosteroids. Antibiotics are useful in treating bacterial infections. Long-acting β2-agonists and anticholinergic inhaled bronchodilators should be preferred over short-acting bronchodilators and oral bronchodilators. Long-term monotherapy with oral or inhaled corticosteroids is not recommended in COPD (70).
Pulmonary rehabilitation

The pulmonary rehabilitation is defined as: “a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies, which include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence of health-enhancing behaviors (71).”

Pulmonary rehabilitation is established and widely accepted as a means of enhancing standard therapy to ease symptoms and optimize function in patients with COPD (71). It is a core component in the management of COPD (71). The primary goals of pulmonary rehabilitation are to reduce symptoms, improve the quality of life, and increase physical and emotional participation in daily activities of life (5,72). To achieve the goals, pulmonary rehabilitation includes patient assessment, exercise training, nutritional support, education about the disease, psychological and social support for the patients and their relatives (6,18,72).

It appears that all patients with COPD benefit from rehabilitation (3,70). It has been demonstrated that the pulmonary rehabilitation in patients with COPD improves exercise capacity and HRQoL, reduces dyspnea, and COPD-related anxiety and depression (71). The numbers of hospitalizations and days in the hospital were also reduced. Ideally, the rehabilitation should involve several types of health professionals, and the program should include exercise training, nutrition counselling, and education (3).

Physical training

Physical training is considered to be the cornerstone of pulmonary rehabilitation (71), and seems to be the best available means of improving muscle function in patients with COPD. Some studies conducted have shown positive effects after participating in pulmonary rehabilitation which included physical training (71,73,74). Physical training results in improving physical capacity, quality of life and physiological improvements in patients with COPD, although the effect on lung function is trivial (75,76). There are different training modalities that have been studied with different results (71,75). Training modalities may consist of endurance or strength training and frequency, duration, intensity and progression of physical activity. It is important to individualize the physical training program since the COPD patients are a heterogeneous group regarding disease severity and age. Besides training, it is also important to educate and give advice and support to patients with COPD regarding the importance of being active in their day
to day life and performing different activities correctly e.g. think about breathing technique, and taking pauses in-between.

**Occupational therapy**

Occupational therapy is a component in multidisciplinary pulmonary rehabilitation. It comprises different aspects of education and training in energy conservation methods, which may reduce energy expenditure and dyspnea perception in certain activities (77). To conserve energy does not necessarily mean doing fewer things but to carry out activities in a different way, and to find different strategies to help manage some of the symptoms that arise (78). The effects of occupational therapy on patients with COPD have been investigated in very few studies. The data that exists indicates positive effects on functional status, and reduced activity limitation (79,80).

**Nutrition**

There is mounting evidence that nutritional intervention in patients with COPD has beneficial effects on body-weight (BW), muscle strength, body composition, respiratory function, and survival (81-84). Schols et al. reported that an increase in body-weight by more than 2 kg / 8 wks. had an independent effect on survival in patients with COPD (46). The risk of having an exacerbation seems to increases when BMI is < 20 kg/m² (61). There are positive effects of dietary intervention during multidisciplinary pulmonary rehabilitation in terms of walking distance, an increase in body-weight and related functions in COPD patients (85,86).

**Energy balance**

To maintain an energy balance, in this group of patients, it is essential to accurately quantify each patient’s energy intake (EI), daily energy expenditure (TEE) and energy requirements. When a person is weight-stable, energy requirement equals total daily energy expenditure. TEE is composed of three parts: resting energy expenditure accounting for about 60%; diet-induced thermogenesis (DIT), accounting for less than 10%; and energy consumed for physical activity making up the rest (approximately 30%) (82).

*Assessment of energy expenditure*

Resting metabolic rate (RMR), which is a synonym for resting energy expenditure has been measured in patients with COPD in several studies using indirect calorimetry (IC) (43,64-66,87,88). RMR is measured in a
resting state that is free of physical and psychological stress, a thermally neutral environment, and a fasting state, i.e. no oral intake for more than ten hours prior to the measurement, to avoid the energy expenditure related to physical activity and DIT (89). IC is the Gold Standard for measuring RMR, but the availability of this method is very limited in clinical praxis. Instead, RMR is often assessed using RMR prediction equations. Table 2 summarizes the RMR prediction equations for healthy adults that are mostly used and those that are COPD disease specific. However, assessing RMR using prediction equations in patients with COPD are found to be inaccurate (87). IC is considered necessary to optimize the nutrition therapy of patients with various pathologies and conditions (89).

Table 2. Summary of RMR prediction equations used often for assessment of RMR in general adult population and for COPD.

<table>
<thead>
<tr>
<th>RMR prediction equations</th>
<th>Year</th>
<th>N, (W/M)</th>
<th>Based on</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mostly used</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harris and Benedict (90)</td>
<td>1919</td>
<td>239, (103/136)</td>
<td>Gender, BW, H, age</td>
</tr>
<tr>
<td>Schofield (91)</td>
<td>1985</td>
<td>7,549 (na)</td>
<td>BW, age</td>
</tr>
<tr>
<td>WHO (92)</td>
<td>1985</td>
<td>11,000 (na)</td>
<td>BW, age</td>
</tr>
<tr>
<td>NNR (93)</td>
<td>2005</td>
<td>na</td>
<td>BW, age</td>
</tr>
<tr>
<td><strong>COPD specific</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moore (94)</td>
<td>1988</td>
<td>43, (10/33)</td>
<td>BW</td>
</tr>
<tr>
<td>Nordenson (95)</td>
<td>2010</td>
<td>41, (30/11)</td>
<td>Fat-free mass</td>
</tr>
</tbody>
</table>

*RMR, resting metabolic rate; N, number of participants; W, women; M, men; BW, body-weight; H, height; na, data not available; WHO, World Health Organization; NNR, Nordic Nutrition Recommendations.*

Objective methods are desirable for assessing TEE in individuals with COPD because individualized nutritional treatment is considered important (96). In clinical settings, TEE is often based on RMR prediction equations and the inclusion of theoretical factors covering disease-specific effects on energy requirements and physical activity (97). However, this method can result in inaccurate assessments of energy requirements (98,99), especially in
patients with COPD because of large individual variations in TEE and physical activity level (PAL) (87,100-102).

Doubly labeled water (DLW) method is considered the “Gold Standard” method for measuring TEE. It is also used as a measure of energy requirement when a person is weight-stable. The DLW method is non-invasive and provides an independent and objective measure of TEE with high precision; DLW also places minimal burdens on the subjects and no restrictions on their activities (103).

The DLW method involves administering a dose of stable isotopes of deuterium (²H) and oxygen (¹⁸O), and subsequently measuring, in urine, the rates of elimination of these isotopes from the body over time. The elimination rate measures the body’s water and water-plus-carbon-dioxide turnover rates; carbon dioxide production can thus be calculated by the difference. The respiratory quotient is set for calculations of the energy equivalence of CO₂ produced, and for western diet, it is 0.85 (104). Until this thesis, to our knowledge, DLW has been used in three studies to measure TEE in patients with COPD (66,87,88). These studies are presented in Table 3. However, the high cost of DLW and the significant technical expertise required for the implementation and analysis of DLW complicates its use in daily clinical settings. Therefore, less expensive and more practical objective methods are required to measure TEE for clinical purposes. In recent years, several motion sensors have been developed to assess TEE and physical activity in different populations including COPD (102,105-107).

Table 3. Doubly labeled water studies conducted for measuring total daily energy expenditure in patients with COPD.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age, yrs.</th>
<th>FEV₁, % predicted</th>
<th>N (W/M)</th>
<th>TEE, kJ</th>
<th>TEE/kg BW, kJ/kg</th>
<th>TEE/kg FFM, kJ/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baarends (66)</td>
<td>67</td>
<td>36</td>
<td>8 (8/0)</td>
<td>10,456</td>
<td>-</td>
<td>227</td>
</tr>
<tr>
<td>Slinde (87)</td>
<td>66</td>
<td>27</td>
<td>10 (5/5)</td>
<td>8000</td>
<td>145</td>
<td>190</td>
</tr>
<tr>
<td>Slinde (88)</td>
<td>64</td>
<td>34</td>
<td>14 (9/5)</td>
<td>7700</td>
<td>146</td>
<td>-</td>
</tr>
</tbody>
</table>

FEV₁, %, Forced expiratory volume in first second % of predicted value; N, number; TEE, total daily energy expenditure; W, women; M, men; BW, Body-weight; FFM, fat-free mass.
The SenseWear® Pro 2 Armband (SWA; BodyMedia Inc., Pittsburgh, PA) is a portable, multi-sensor motion sensor that integrates a biaxial accelerometer and physiological sensors, and is worn on the upper right arm. This monitor can be used to calculate the TEE and activity energy expenditure (AEE) of individuals based on their BW, height, handedness, and smoking status. It has been used to measure AEE in COPD patients in free-living state, (100-102,108), however, for measuring TEE, it has primarily been used in laboratory settings (106,107,109).

The ActiHeart (AH; Cambridge Neurotechnology Ltd., Papworth, UK) monitor is a single-piece combined heart rate recorder and an accelerometer designed to be worn on the chest with two ECG electrodes. The AH monitor provides estimates of TEE, RMR, AEE, DIT, and PAL based on the user’s age, gender, weight, and height (110), but has not previously been validated in COPD patients.

Assessment of energy intake

Assessment of self-reported EI is essential in nutritional intervention as EI is one of the important components in energy homeostasis (111). EI can be assessed using different dietary assessment methods such as diet history, recall, weighed records, and food diaries (112). Diet history and recall are retrospective methods, whereas, weighed records and food diaries are prospective methods of dietary assessment.

Several validation studies of dietary assessment methods have been conducted using different reference methods with varying results (112). The DLW method is also used as a criterion method for validating reported EI as assessed by dietary assessment methods. Validating reported EI methods using TEE measured by DLW as the criterion method is based on the fundamental principle that in energy balance, TEE is equivalent to EI (103).

In studies concerning patients with COPD, EI has been assessed using different methods such as diet history and 7-day food diaries (43,87). The diet history method has been validated using DLW in healthy subjects only (113,114).
Assessment of energy requirement

The assessment of energy requirement is pivotal in nutritional intervention. Several methods are used to assess the energy requirement. TEE measured by DLW method is also used as a measure of energy requirement when a person is weight-stable. Different motion sensors are also used for assessment of TEE/energy requirement (102,105-107). Other studies have calculated energy requirement in COPD patients using predicted RMR and predefined activity factors (115). However, the access to DLW method or motion sensors in the clinical praxis is very limited. Thus the methods that are readily available are RMR prediction equations and assessment of physical activity.

Physical activity is an important component in TEE and accounts for approximately 30% of TEE (82). In COPD patients, physical activity has been assessed using different devices, from simple pedometers to more complex motion sensors (38,105,107). Pedometers are inexpensive, feasible, and easily available devices. The Yamax Digi-Walker SW-200 (Yamasa Tokei Keiki Co. Ltd, Tokyo, Japan) is a pedometer that is widely used in research and has been shown to be valid (116,117). It is a mechanical, uniaxial, spring-levered pedometer that shows the accumulated numbers of steps taken per day, and is worn on the anterior side of the hip. The numbers of steps taken per day have been translated to define physical activity and subsequently classify if a person is sedentary or active (118).
Rationale for this thesis

In Sweden, many patients with COPD are under-weight and in need of nutritional treatment. The frequency and distribution of under-weight in COPD patients with different severity, and gender differences, had not been clearly addressed in population-based studies. For a successful nutritional treatment, it is essential to assess the COPD patient’s energy expenditure, intake, and requirement, with objective validated methods. Currently, these components of energy balance are assessed by a variety of methods that are based on non-COPD groups which may lead to discrepancies and inaccuracy in the estimated values. Furthermore, in the clinical setting, the nutritional care provider faces the dilemma, as to which method to use. There is lack of studies that have validated methods for estimating the aforementioned components of energy balance in hospitalized as well as non-hospitalized patients with COPD. There is also lack of consensus regarding the energy requirement guidelines for patients with COPD. The increase in COPD prevalence, morbidity and mortality has appeared most pronounced in women, but COPD research focusing on women has so far been limited. These circumstances constitutes the scientific and clinical rationale and motivation for the present thesis.


**Aims of the thesis**

The overall objective was to validate and increase the knowledge of methods which are reliable, cost-effective, and simple to use for assessment of energy expenditure, energy requirement and energy intake in women with COPD. Further, to gain insight into energy expenditure and requirement, we explored all available data on energy expenditure measured by doubly labeled water in patients with COPD. We also examined the BMI and clinical characteristics of women and men with COPD compared to the control subjects in a population-based study.

**Specific aims**

**Paper I**

To validate two motion sensors - SenseWear Armband and ActiHeart for assessment of total energy expenditure in non-hospitalized women with COPD, using the doubly labeled water as the reference method.

**Paper II**

To validate diet history interview and 7-day food record for assessing energy intake, in non-hospitalized women with COPD, by comparing it with the doubly labeled water method.

**Paper III**

To assess energy requirement using pedometer-determined physical activity level in combination with common resting metabolic rate equations in non-hospitalized women with COPD, by comparing it with the doubly labeled water method.

**Paper IV**

To compile all available data on energy expenditure measured by doubly labeled water method in patients with COPD, in order to increase the current knowledge of energy requirement for clinical use in patients with COPD.

**Paper V**

To compare subjects with and without COPD, regarding BMI and clinical characteristics from the population-based OLIN study. Further, to compare women and men with COPD with regards to BMI and clinical characteristics.
Materials and methods

A short description of material and methods are given here. More extensive details are given in the respective papers.

All the studies were approved by the Regional Ethics Committee at Umeå University and were carried out according to the Declaration of Helsinki. Written informed consent was obtained from each of the subjects before their participation in the study.

Papers I – III

Study design and protocol

These validation studies were conducted in the Department of Medicine, the Respiratory Medicine and Allergy Unit, and the Clinical Research Center at Umeå University Hospital in Umeå, Sweden. The study time was two consecutive weeks for each patient. Table 4 presents an overview of the data collection. TEE was assessed in 19 non-hospitalized women with COPD, using 14 days DLW analysis. Simultaneously, the TEE was also determined by two different motion sensors (SenseWear Armband and ActiHeart), and PAL was determined with a pedometer. EI was assessed by diet history interview and 7-day food record.

The study started with a visit to the hospital. There a blood sample was collected from each patient for measurements of arterial oxygen tension (pO2) and arterial carbon dioxide tension (pCO2). Body-weight (BW), height, RMR and body composition were measured at the beginning of the study. BW was again measured at the end of the study. In total, each visit lasted 5-6 hours. A home visit was performed between days 7-9 of the study period. The purpose of the home visit was to download data, charge or change the batteries in each of the two monitors, and ensure the appropriate collection and storage of urine samples. Pulmonary function tests were conducted within the first three months following the 14-day study period.
Table 4. Overview of data collection during 14 day study period in papers I-III.

<table>
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<th>Procedures a</th>
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<td>Body-weight</td>
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<td>Arterial blood gas</td>
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<td>Oxygen saturation at rest</td>
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<tr>
<td>Resting metabolic rate using indirect calorimetry</td>
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<tr>
<td>Total energy expenditure using Doubly labeled water</td>
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<tr>
<td>Total energy expenditure using SenseWear Armband b</td>
<td>x</td>
<td>x</td>
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<td>x</td>
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<tr>
<td>Total energy expenditure using ActiHeart b</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td>x</td>
<td>x</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Urine samples</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td>x</td>
<td>x</td>
<td>x</td>
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<td>Energy intake assessed by Diet history interview c</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Energy intake assessed by 7-day food diary c</td>
<td>x</td>
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<tr>
<td>Body composition using DXA d</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td>x</td>
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<tr>
<td>Pedometer d</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td>x</td>
<td>x</td>
<td>x</td>
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<td>x</td>
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<tr>
<td>Home visit, single</td>
<td>x</td>
<td>x</td>
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</tbody>
</table>

a Procedures included in all papers, unless stated otherwise; b Included in Paper I; c Included in Paper II; d Included in Paper III
**Materials and methods**

**Population**

Nineteen women with COPD attending the outpatient clinic, at the Department of Respiratory Medicine and Allergy, University Hospital, Umeå, were identified and recruited after fulfilling the inclusion criteria.

**Inclusion criteria**

Patients with clinically stable COPD, with documented post bronchodilator FEV$_1$/FVC < 0.7 [Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD), Stage 2-3] (119) and with BMI between 18.5 – 30 kg/m$^2$ (120) were included.

**Exclusion criteria**

Any oxygen therapy or insulin treated diabetes or thyroid dysfunction or myopathic- or neoplastic disease.

**Anthropometry**

BW and height were measured at the start of the study, and BW was measured again at the end of the 14-day study period. The weight history of each patient for the past six months was also obtained. BMI was then calculated based on these measurements (BW in kg/ height in m$^2$).

**Pulmonary function measurements**

Dynamic and static pulmonary function tests were performed. Oxygen saturation was measured during periods of rest and activity using a pulse oximeter. Arterial pO$_2$ and pCO$_2$ was also measured.

**Energy expenditure**

*Doubly Labeled Water Method*

Total energy expenditure was measured using doubly labeled water. The DLW method involves administering a dose of stable isotopes of deuterium ($^{2}$H) and oxygen ($^{18}$O) and subsequently measuring the rates of elimination of these isotopes from the body over time. On day one, each patient ingested a weighed dose of DLW [mixture of deuterated water that was enriched with $^{18}$O (0.05 g deuterium oxide ($^{2}$H$_2$O) and 0.10 g $^{18}$O-containing water ($^{18}$O) per kg of body-weight]. A urine sample was collected from each patient for
determination of background isotope enrichment before ingestion of DLW. The patients’ collected urine samples on days 2, 3, 4, 8, 13, 14, and 15. Urine samples were analyzed in triplicate using a Finnigan MAT Delta Plus Isotope-Ratio Mass Spectrometer (Figure 1A). TEE (kJ d\(^{-1}\)) was calculated using the multipoint method by linear regression based on the difference between the elimination constants of deuterium and oxygen-18, with the assumption of fractionation. The relationship between pool size deuterium (N\(_D\)) and pool size oxygen-18 (N\(_O\)) was used as a quality measurement. The acceptable range of this relationship (ND/NO) has been proposed by the IAEA to be between 1.015 and 1.060 (121). The respiratory quotient was set at 0.85 for calculations of the energy equivalence of CO\(_2\) produced (104).

**Resting metabolic rate**

The resting metabolic rate was measured by indirect calorimetry using a ventilated hood system (Figure 1B). Patients arrived on the test day in a fasting state, and the resting metabolic rate of each patient was measured for 30 minutes after the patients had rested in a supine position for 30 minutes. Prior to each measurement, the equipment was calibrated with gas mixtures (O\(_2\) and CO\(_2\)) according to the manufacturer’s instructions. The results shown are based on the last 25 minutes of measurement.

**Activity energy expenditure**

For the purposes of the paper I-III, AEE was defined as the energy that an individual expends during all of the movements that were performed during the daily study period. The criterion values for AEE were calculated as TEE – RMR, which were measured using the DLW method (TEE) and indirect calorimetry (RMR).

**Smoking habits**

Information about smoking habits was collected through interviews and was recorded as the number of pack-years.

**Sample power**

The sample power was calculated using Sample Power version 2.0 (SamplePower®; Statistical Package for the Social Sciences; SPSS Inc., Chicago, Illinois, USA). The sample power calculation was based on the primary objective, to validate energy intake as estimated from diet history and 7-day food diaries compared with energy expenditure measured with doubly labeled water. A sample size of 19 subjects was calculated to have
Materials and methods

80% power of an approximately 12% underestimation of reported energy intake (2-tailed alpha error of 0.05).

Paper I

In this paper, TEE and AEE was also determined by two different motion sensors, SenseWear Armband and ActiHeart.

**SenseWear® Pro 2 Armband**

The SenseWear® Pro 2 Armband is a portable, multi-sensor body monitor that integrates a biaxial accelerometer and physiological sensors (Figure 1C). This monitor can be used to calculate the TEE and AEE of individuals for whom the body-weight, height, handedness, and smoking status are known. Each patient received a SWA at the time of her first visit, and was instructed to wear it at all times, both day and night, except during bathing. The data were sampled in 1-minute intervals and were used in combination with each patient’s characteristics to estimate TEE using proprietary algorithms. Data were evaluated using InnerView Professional software, versions 5.1 (SWA5) and 6.1 (SWA6).

**ActiHeart**

The ActiHeart monitor is a heart rate recorder with an integrated accelerometer that can be used to calculate TEE, RMR, AEE, diet-induced thermogenesis, and PAL based on the user’s age, gender, weight, and height (109) (Figure 1D). All patients were given an AH at the time of their first visit. Prior to performing long-term recordings of the patients, a signal test and a step test were performed in accordance with the manufacturer’s instructions to ensure the correct placement of the device and to synchronize the AH at an individual level. The data were sampled in 1-minute intervals and were used in combination with each patient’s characteristics to estimate TEE and AEE using proprietary algorithms. Patients were instructed to wear the AH at all times, including at night. However, wearing this device while bathing was optional.

Thorough oral and written instructions regarding the appropriate use of SWA and AH were provided. The patients were also instructed to keep a record of the times that they were not wearing these devices, including a list of the activities performed during those periods.
Activity energy expenditure assessed by SWA and AH

The AEE was determined by two methods.

Method 1

AEE was estimated from SWA as TEE – RMR. TEE estimates were derived from SWA, whereas, RMR estimates were derived from the Harris-Benedict equation for women (88), since SWA assess only TEE and not RMR. AEE was also calculated from AH as TEE – RMR, which was estimated from AH. Thus, AH provides estimations of both TEE and RMR.

Method 2

AEE was also estimated from SWA (TEESWA – RMR) and AH (TEEAH – RMR) using RMR measured by indirect calorimetry. Thus RMR from indirect calorimetry was used in all the calculations of AEE.
Materials and methods

Figure 1A. Isotope-Ratio Mass Spectrometer

Figure 1B. Indirect Calorimetry

Figure 1C. SenseWear Pro 2 Armband
Materials and methods

Figure 1D. ActiHeart

Figure 1E. Pedometer

Figure 1F. Dual-energy X-ray Absorptiometry
Materials and methods

Paper II

In this paper, energy intake was assessed by diet history interview and 7-day food diary and the EI was calculated using the nutrient software program DIETIST using the “Swedish Food Data Base” from the National Food Administration (Livsmedelverket, 2009).

Diet history interview

Energy intake for each patient was estimated from diet history interview that was conducted by an experienced dietitian during the hospital visit on day 1. The interview included questions regarding habitual intake/eating patterns and the types, quantities and frequency of food items and fluid consumption. The food items and fluids consumed ≥ 2 times/month at each meal were registered. The dietary intake data obtained from the diet history interviews were then converted into seven days to represent a week. A Swedish meal model booklet comprising different food portion pictures was used as an aid to assess the amount of food consumed as correctly as possible.

7-day food diary

For the 7-day food diary, the patients were provided with a food registration form to record all food items and fluids they consumed for the first seven days of the study period. Thorough verbal and written instructions were provided to patients regarding how to record their food consumption. To assess portion sizes, the patients were requested to use meal model pictures and household measures such as deciliters, tablespoons or drinking glasses. During the home visits, the 7-day food diaries were, prior to their collection, thoroughly monitored with the patients to ensure the accuracy of the obtained information.

Reporting accuracy of energy intake

The accuracy of both methods for reporting energy intake was defined as the ratio of energy intake to the total energy expenditure (EI/TEE). Based on 95% confidence limits for the EI/TEE ratio, the patients were classified as valid-reporters (VR), under-reporters (UR) or over-reporters (OR), as has been suggested (113). Patients whose EI/TEE values were between 0.79–1.21 were defined as VR, < 0.79 as UR and > 1.21 as OR (114).
Materials and methods

**Paper III**

**Prediction Equations**

In this study the RMR was also estimated from six different commonly used prediction equations for women:

1. Harris-Benedict (90)
2. Schofield (91)
3. WHO, 1985 (92)
4. Nordic Nutrition Recommendations (NNR), 2012 (93)
5. Moore (94)
6. Nordenson (95)

**Physical activity level**

The criterion physical activity level (PAL) was calculated from energy expenditure measured by DLW ($\text{TEE}_{DLW}$) method and RMR measured by indirect calorimetry ($\text{RMR}_{IC}$) ($\text{PAL} = \frac{\text{TEE}_{DLW}}{\text{RMR}_{IC}}$).

**Pedometer**

PAL was also determined by a pedometer, the Yamax Digi-Walker SW-200 (Figure 1E). The pedometer was placed on the belt or waistband, in the midline of the thigh, consistent with the manufacturers’ recommendations. The patients were instructed to wear the pedometer during the day time for 14 days except during shower/bathing. Thorough oral and written instructions regarding the appropriate use of the pedometer were provided. The patients were also instructed to keep a record of the times that they were not wearing this device, including a list of the activities performed during those periods.

Accumulated numbers of steps taken until the end of the study period were registered and an average number of steps/day were calculated. Pedometer-determined PAL was calculated in two stages. First, the patients were classified into different activity categories based on their average number of
steps taken/day as proposed by others (118). In the second stage, PAL values were estimated according to the patient’s physical activity category (122).

Each above mentioned RMR prediction equation was multiplied by pedometer-determined PAL for an assessment of energy requirement (RMR from prediction equations x PAL pedometer-determined). The accuracy of individually predicted energy requirement was defined as the percentage of participating individuals whose predicted energy requirement was within ± 10% of measured TEE (123).

**Body composition**

Fat-free mass was measured at the start of the study by dual-energy X-ray absorptiometry (DXA), total body scanner (Lunar Prodigy, version 13.31, Scanex Medical Systems, Helsingborg, Sweden) (Figure 1F).

**Paper IV**

**Study design**

This study is based on the studies reporting TEE measured by DLW method conducted in patients with COPD in Sweden. We searched Pub Med for all the studies reporting TEE measured by DLW method in patients with COPD, and found four studies (66,87,88,124). Three studies were conducted in Sweden. The studies are referred to in chronological order as study-1 (87), study-2 (88), and study-3 (124). All relevant data from study 1-3 were acquired for analysis. As regards to the other study (66), at present, these data have been requested, but have not become available to be included in the analysis.

**Subjects**

Study-1 included ten patients with BMI ≤ 20 kg/m², and study-2 comprised of 15 patients with BMI < 21 kg/m². All patients in studies 1 and 2 had severe and stable COPD with FEV₁ < 50% predicted using the criteria from The European Respiratory Society (18). In study-3, 19 women with stable COPD, GOLD 2-3 (FEV₁ % of predicted value <80 – 30 %) (119), and BMI 18.5 – 30 kg/m² were included (120). Therefore, the present study includes 44 patients (34 women and ten men) with stable COPD, FEV₁ < 80 % predicted, and BMI ≤ 30 kg/m².
**Materials and methods**

**Pulmonary function tests**

In study-1 & 2, the pulmonary tests were performed using a Vitalograph spirometer (Selefa, Buckingham, Ireland) before and 15 min after inhalation of 1 mg terbutaline. In study-3, all the patients had COPD diagnosed by clinical investigation as well as post-bronchodilator spirometry with FEV<sub>1</sub>/FVC < 0.7 prior to their inclusion in the study. For the study purpose, dynamic and static pulmonary function tests were performed.

In the present study, GOLD spirometry criteria was used to define disease severity (3): GOLD 2 (moderate), 50% ≤ FEV<sub>1</sub> < 80 % of predicted values; GOLD 3 (severe), 30% ≤ FEV<sub>1</sub> <50 % of predicted values; GOLD 4, (very severe), FEV<sub>1</sub> < 30 % of predicted values.

**Body composition**

Body-weight (BW) and height was measured, and BMI was then calculated based on these measurements (BW in kg/height in m<sup>2</sup>). Body composition was measured by DXA using a total body scanner in study 1-3. Fat-free mass index was calculated as fat-free mass in kg/height in m<sup>2</sup>.

The BMI cut-off for defining underweight was < 22.5 kg/m<sup>2</sup> (58), and for FFMI, the cut-off for depletion was ≤ 15 (women) or ≤ 16 (men) kg/m<sup>2</sup> (44).

**Energy expenditure**

**Resting metabolic rate**

The RMR was measured by indirect calorimetry using a ventilated hood system in all the three studies. In Study-1 & 3 Deltatrac™ II Metabolic Monitor was used, and in study-2 the equipment used was a Medical Graphics Corp. cardio pulmonary exercise system CPX. Patients arrived on the test day in a fasting state, and the RMR of each patient was measured for 20-30 minutes after the patients had rested in a supine position for 30 minutes. The RMR per kg BW per day (daily RMR, kJ/BW, kg), and RMR per kg FFM per day (daily RMR, kJ/FFM, kg) were calculated.

**Total daily energy expenditure**

The TEE was measured using the DLW method as described earlier in the method section (86,87,123). The analysis of the DLW in all the three studies were conducted in the same laboratory. The TEE per kg BW per day (daily
Materials and methods

TEE, kJ/BW, kg), and TEE per kg FFM per day (daily TEE, kJ/FFM, kg) were calculated.

**Activity energy expenditure and physical activity level**

In the present study, activity energy expenditure (AEE) was defined as the energy expenditure for all the movements that were performed daily. The AEE was calculated as the difference between TEE and RMR (AEE = TEE – RMR), and PAL as TEE/RMR.

**Paper V**

**Study population**

The subjects in this study are a part of Obstructive Lung Disease in Northern Sweden (OLIN) studies. In the present study, based on data collected in 2005, a total of 1641 subjects participated. Of these, 1626 (99%) (COPD, n=635; non-COPD, n= 991) had complete data on anthropometry, spirometry, and structured interview, and were included in this study.

**Questionnaires**

The structured interview included validated questions regarding respiratory symptoms (125-128). The modified Medical Research Council Dyspnea Scale (mMRC) was included in the questionnaire to grade dyspnea, scale 0–4 (129). Also, data on co-morbidities, medication and smoking habits were included.

**Anthropometry**

Body-weight and height were measured before spirometry was conducted. BMI was calculated based on these measurements (Body-Weight in kg/height in m²). BMI was then categorized as follows (58):

- **Under-weight**, BMI < 22.5 kg/m²
- **Normal-weight**, BMI 22.5 – 24.9 kg/m²
- **Over-weight**, BMI 25 – 29.9 kg/m²
- **Obese**, BMI ≥ 30 kg/m²
**Definitions**

Clinically significant dyspnea was defined as the mMRC score of ≥ 2. Smoking habits were classified as non-smokers, ex-smokers (stopped since at least one year) and the current smokers. The pack-years of smoking were calculated [(number of cigarettes smoked/day x no. of years smoked)/20].

**Spirometry and classification of lung function**

The pulmonary function tests were carried out using a dry volume spirometer, the Vicatest 5, in accordance with the American Thoracic Society guidelines (130). The highest value of forced vital capacity (FVC) or slow vital capacity (SVC), pre- or post- reversibility test was used as a measure of vital capacity (VC). Similarly, the highest value of FEV₁ pre- or post-reversibility test was used. Reversibility test was performed if FEV₁ was < 80 % of the predicted value or if the FEV₁/VC was < 0.70.

COPD was defined as post-bronchodilator FEV₁/VC < 0.70. The severity of COPD was classified according to the GOLD spirometry criteria based on FEV₁ % of predicted value: GOLD 1–4 (3). The OLIN lung function reference values, based on healthy nonsmokers, were used (131).

The non-COPD reference population, defined as FEV₁/VC ≥ 0.70, was further categorized into the subjects with normal lung function (NLF, FEV₁/VC ≥ 0.70 and VC > 80 % predicted), and the subjects with restrictive spirometry pattern (RSP, FEV₁/VC ≥ 0.70 and VC < 80 % predicted).

**Statistics**

The data were analyzed in all papers using statistical program SPSS version 19.0 (paper I), version 21.0 (paper II & III), and version 24.0 (paper IV & V). The overview of statistical models used in the analysis are shown in Table 5. The level of significance was set at P-value of < 0.05.

Descriptive statistics, such as means, standard deviations, and minimum and maximum values were used across the papers I-V.

Paired t-test was used in paper I-III to assess the differences between the reference method, DLW and the methods to be validated. To determine the strength of the relationship between the reference method, DLW and the methods to be validated, Pearson’s correlation coefficient was calculated (132). Intraclass correlation coefficient (ICC) assuming a two-way analysis was used to examine the degree of agreement between the DLW method and
the methods to be validated. For ICC analysis, the closer the correlation is to 1.0, the lower the within-subject variance and the greater the concordance between the estimates (133). To examine the degree of systematic bias and to calculate the limits of agreement between the DLW method and the methods to be validated Bland-Altman plots were constructed (134).

Table 5. Overview of statistical models used for analysis in papers I-V.

<table>
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<tbody>
<tr>
<td><strong>Parametric tests</strong></td>
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<td></td>
</tr>
<tr>
<td>Paired t-test</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Independent t-test</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Pearson’s correlation coefficient</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Intraclass correlation coefficient</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
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<tr>
<td>ANOVA</td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
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<tr>
<td>Multiple linear regression</td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
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<tr>
<td>Post-hoc analysis (Bonferroni)</td>
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<td></td>
<td></td>
<td>x</td>
<td></td>
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<tr>
<td><strong>Non-parametric tests</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chi-square / Fisher’s exact test</td>
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<td></td>
<td></td>
<td>x</td>
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</tr>
</tbody>
</table>

In paper IV & V, Pearson’s correlation coefficient was calculated to investigate the correlation between the variables. Independent t-tests were performed when group means of the continuous variables were compared, and analysis of variance used when appropriate. Multiple linear regression analysis were used to identify the correlates of outcome measures. In paper V, the differences in the categorical outcomes were analyzed with chi-square or Fischer’s exact tests when appropriate. When multiple comparisons were performed, Bonferroni corrected significant values were presented.
Results

Main results are described below. For details see articles/ manuscript.

Papers I-III

Patient characteristics

The general characteristics of the participating women with COPD are shown in Table 6. All had smoked between 14 and 42 pack-years. Thirteen women (68%) had quit smoking, and six were current smokers. Twelve women had a BMI < 25 kg/m². The BW did not change in any of the patients during the study period. Eighteen women had an FFMI below normal value, ≥ 15 kg/m² (44). Pulmonary function tests were performed within the 3-months following the 14-day study period in 16 of the women who participated in the study. Of the three remaining patients, one died of heart failure; one moved to Southern Sweden, and one refused to participate.

Energy expenditure measured by DLW and RMR measured by indirect calorimetry was collected from all 19 patients, and is shown in Table 7. There was a considerable variation in TEE and RMR. The overall compliance with regards to participation and execution of different tasks in this study was excellent.

Paper I (Energy expenditure)

The patients wore the SWA and AH as instructed. No large gaps (> 15 minutes) were recorded, and the brief gaps in the data were auto-filled by the SWA and AH. Two women had registered SWA and AH data for only 13 days; therefore, an average of 13 days was used for all of the analyses. The measured ND/NO values obtained using the DLW method were between 1.018 and 1.048.

Total energy expenditure

The estimates of TEE obtained using the DLW, SWA version 5.1 and 6.1, and AH methods (TEE<sub>DLW</sub>, TEE<sub>SWA5</sub>, TEE<sub>SWA6</sub>, respectively TEE<sub>AH</sub>) are shown in Table 8. A considerable amount of variation was observed in TEE measured by different methods within this COPD group. Assessments of TEE using SWA 5.1 showed an overestimation by 0.3% compared with the result obtained using the criterion method, whereas both the SWA 6.1 and AH methods underestimated TEE by approximately 9%. The difference of means
using paired t-test between the criterion method and the SWA 5.1, SWA 6.1, and AH methods are presented in Table 7. The difference of means of TEE assessed by DLW and SWA 5.1 was least and non-significant (Table 8).

Table 6. General characteristics of women with COPD.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean ± SD</th>
<th>Min-Max</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>19</td>
<td>69.2 ± 6.0</td>
<td>59.7-80.0</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>19</td>
<td>63.5 ± 10.7</td>
<td>46.8-88.0</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>19</td>
<td>24.5 ± 3.5</td>
<td>18.5-30.0</td>
</tr>
<tr>
<td><strong>% IBW</strong></td>
<td>19</td>
<td>99.0 ± 14.0</td>
<td>75-124</td>
</tr>
<tr>
<td><strong>FFMI, kg/m²</strong></td>
<td>19</td>
<td>12.6 ± 1.3</td>
<td>10.3-16.0</td>
</tr>
<tr>
<td><strong>Number of pack years</strong></td>
<td>19</td>
<td>27.7 ± 9.0</td>
<td>14-42</td>
</tr>
<tr>
<td><strong>Arterial pCO₂, kPa</strong></td>
<td>16</td>
<td>5.2 ± 0.6</td>
<td>4.3-6.7</td>
</tr>
<tr>
<td><strong>Arterial pO₂, kPa</strong></td>
<td>16</td>
<td>10.2 ± 2.9</td>
<td>4.4-18.4</td>
</tr>
<tr>
<td><strong>FEV₁/FVC, liters</strong></td>
<td>16</td>
<td>0.43 ± 0.12</td>
<td>0.24-0.65</td>
</tr>
<tr>
<td><strong>FEV₁, % of predicted value</strong></td>
<td>16</td>
<td>56.0 ± 15.0</td>
<td>30-78</td>
</tr>
<tr>
<td><strong>DLCO, % of predicted value</strong></td>
<td>16</td>
<td>47.0 ± 13.0</td>
<td>28-71</td>
</tr>
<tr>
<td><strong>IC, % of predicted value</strong></td>
<td>16</td>
<td>95.0 ± 20.0</td>
<td>60-134</td>
</tr>
</tbody>
</table>

*BMI, body mass index; IBW, ideal body-weight; FFMI, fat-free mass index; FEV₁, forced expiratory volume in 1st s; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; IC = inspiratory capacity.*
Table 7. Energy expenditure in women with COPD (N = 19).

<table>
<thead>
<tr>
<th>Energy expenditure, kJ-d</th>
<th>Mean ± SD</th>
<th>Min-Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEE measured by DLW</td>
<td>7967 ± 1090</td>
<td>5318–10258</td>
</tr>
<tr>
<td>RMR measured by IC</td>
<td>4768 ± 601</td>
<td>3617-6248</td>
</tr>
<tr>
<td>AEE (TEE – RMR)</td>
<td>3199 ± 693</td>
<td>1701-4594</td>
</tr>
</tbody>
</table>

TEE, total energy expenditure; DLW, doubly labeled water; RMR, resting metabolic rate; IC, indirect calorimetry; AEE, activity energy expenditure.

The correlations between the criterion method (TEE\textsubscript{DLW}) and the TEE\textsubscript{SWA5}, TEE\textsubscript{SWA6}, and TEE\textsubscript{AH} methods were all statistically significant (Figure 2 A-C). The agreement between the criterion method and the SWA 5.1, SWA 6.1, and AH methods with regard to the estimates of TEE as analyzed by ICC are shown in Table 7. Bland-Altman plots for TEE (Figure 3 A-C), as estimated by SWA 5.1, SWA 6.1, and AH revealed that the values were evenly distributed around the mean. No systematic bias was present in these plots, indicating that no significant relationship exists between the magnitude of energy expenditure and the differences in energy expenditure between the two methods.
Table 8. Energy expenditure estimates from the criterion and SWA, and AH methods using different statistical analysis in women with COPD (N=19).

<table>
<thead>
<tr>
<th>Total energy expenditure</th>
<th>Mean ± SD kJd⁻¹</th>
<th>Difference of the mean ± SD a kJd⁻¹</th>
<th>P-values</th>
<th>Intraclass correlations coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Criterion (DLW)</strong></td>
<td>7967 ± 1090</td>
<td></td>
<td></td>
<td>ICC 0.90, 95% CI 0.47 - 0.90</td>
</tr>
<tr>
<td><strong>SWA₅</strong></td>
<td>7988 ± 945</td>
<td>- 21 ± 726</td>
<td>0.90</td>
<td>ICC 0.66, 95% CI 0.02 - 0.88</td>
</tr>
<tr>
<td><strong>SWA₆</strong></td>
<td>7258 ± 1027</td>
<td>709 ± 667</td>
<td>0.001</td>
<td>ICC 0.61, 95% CI 0.05 - 0.85</td>
</tr>
<tr>
<td><strong>AH</strong></td>
<td>7260 ± 1048</td>
<td>707 ± 786</td>
<td>&lt; 0.001</td>
<td>ICC 0.61, 95% CI 0.05 - 0.85</td>
</tr>
</tbody>
</table>

a criterion – test method.

ICC, intraclass correlation coefficient; DLW, doubly labeled water; SWA, SenseWear Armband version 5.1 and 6.1; AH, ActiHeart.
Results

Figure 2. Pearson’s correlations between the mean TEE measured by the DLW method (TEE\textsubscript{DLW}) and by (A) the SenseWear Armband, version 5.1 (TEE\textsubscript{SWA5}), (B) the SenseWear Armband, version 6.1 (TEE\textsubscript{SWA6}), and (C) the ActiHeart (TEE\textsubscript{AH}) method in 19 women with COPD.
Figure 3. Bland-Altman plots showing the differences in the mean TEE between the DLW method (TEE_{DLW}) and (A) the SenseWear Armband, version 5.1 (TEE_{SWA5}), (B) the SenseWear Armband, version 6.1 (TEE_{SWA6}), and (C) the ActiHeart (TEE_{AH}) monitor in 19 women with COPD.
Results

Activity energy expenditure

AEE assessed by criterion method (DLW and IC) and by SWA and AH, using two different methods are shown in Table 9.

Method 1

There was a large variation in AEE estimated by the DLW (1701-4594 kJd⁻¹), SWA5.1 (1495-4508 kJd⁻¹), SWA6.1 (507-3371 kJd⁻¹) and AH (827-3500 kJd⁻¹) methods. Compared with the criterion method, SWA 5.1 underestimated AEE values by approximately 12%, whereas the SWA 6.1 and AH methods underestimated AEE values by about 35%.

Method 2

A considerable variation was seen in AEE estimated by SWA5.1 (1852-4806 kJd⁻¹), SWA6.1 (913-3880 kJd⁻¹) and AH (1058-4040 kJd⁻¹) methods. The difference of the means between the criterion method and test methods for assessment of AEE was similar to that of TEE.

The ICC analysis showed a better agreement between the criterion method and the test methods using measured RMR by indirect calorimetry in all the analysis of AEE than using estimated RMR by Harris-Benedict equation for AEE calculations by SWA.
Table 9. Activity energy expenditure estimates from the criterion, SWA, and AH methods using different statistical analysis in women with COPD (N=19).

<table>
<thead>
<tr>
<th>Activity energy expenditure</th>
<th>Mean ± SD</th>
<th>Difference of the means ± SD</th>
<th>Pearson’s correlation</th>
<th>Intraclass correlations coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>kJd⁻¹</td>
<td>kJd⁻¹</td>
<td>r</td>
<td>ICC</td>
</tr>
<tr>
<td><strong>Method 1</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Criterion (TEE&lt;sub&gt;DLW - RMR&lt;sub&gt;IC&lt;/sub&gt;)</td>
<td>3199 ± 693</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWA5</td>
<td>2814 ± 810</td>
<td>385 ± 686</td>
<td>0.03</td>
<td>0.59</td>
</tr>
<tr>
<td>SWA6</td>
<td>2085 ± 810</td>
<td>1114 ± 634</td>
<td>&lt;0.001</td>
<td>0.65</td>
</tr>
<tr>
<td>AH</td>
<td>2070 ± 709</td>
<td>1128 ± 586</td>
<td>&lt;0.001</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Method 2</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Criterion (TEE&lt;sub&gt;DLW - RMR&lt;sub&gt;IC&lt;/sub&gt;)</td>
<td>3199 ± 693</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWA5</td>
<td>3220 ± 791</td>
<td>-21 ± 726</td>
<td>0.90</td>
<td>0.71</td>
</tr>
<tr>
<td>SWA6</td>
<td>2490 ± 783</td>
<td>709 ± 667</td>
<td>&lt;0.001</td>
<td>0.75</td>
</tr>
<tr>
<td>AH</td>
<td>2490 ± 829</td>
<td>709 ± 786</td>
<td>0.001</td>
<td>0.65</td>
</tr>
</tbody>
</table>

<sup>a</sup> criterion – test method;  <sup>b</sup> RMR estimates for SWA5 and SWA6 were calculated using Harris-Benedict BMR equation;  <sup>c</sup> RMR measured by indirect calorimetry was used in all calculations.

ICC, intraclass correlation coefficient; TEE<sub>DLW</sub>, total energy expenditure measured by doubly labeled water; RMR, resting metabolic rate measured by indirect calorimetry; SWA5, SenseWear Armband version 5.1; SWA6, SenseWear Armband version 6.1; AH, ActiHeart.


**Paper II (Energy intake)**

The EI assessed by diet history and the 7-day food diaries were collected from all 19 patients. The TEE estimates from DLW, and EI assessed with diet history (EI\textsubscript{DH}) and 7-day food diaries (EI\textsubscript{FD}) are shown in Table 10. The EI varied within this group. The correlation was weak between TEE\textsubscript{DLW} and EI\textsubscript{DH} ($r = -0.05$, $P = 0.85$) and between TEE\textsubscript{DLW} and EI\textsubscript{FD} ($r = 0.19$, $P = 0.45$).

Paired t-test analysis between the criterion method (TEE\textsubscript{DLW}) and EI\textsubscript{DH}, and EI\textsubscript{FD} are shown in Table 10. The diet history underestimated reported EI by 28% compared with the criterion method, DLW; and the 7-day food diaries underestimated reported EI by approximately 20%. The ICC analysis showed weak agreement between TEE\textsubscript{DLW} and EI\textsubscript{DH} (Table 10) and between TEE\textsubscript{DLW} and EI\textsubscript{FD} (Table 10). In the Bland-Altman plots (Figures 4 A-B), the values were evenly distributed around the mean difference. There was a trend toward a relation between the magnitude of energy intake and the difference in energy intake as assessed by diet history and 7-day food diary, respectively. The higher the energy intake as estimated from diet history, the greater the difference, whereas with the 7-day food diaries, the lower the energy intake, the greater the difference.

More women were identified as valid-reporters based on their 7-day food diaries than on their diet histories (63% compared with 32%, $P = 0.08$). The mean EI/TEE ratio for diet history was $0.73\pm0.16$ ($P < 0.001$), and the ratio was $0.81\pm0.23$ ($P < 0.001$) for the 7-day food diaries. The EI/TEE ratios for diet history and the 7-day food diaries were significantly correlated only to BMI ($r = -0.47$, $P = 0.04$ and $r = -0.50$, $P = 0.03$, respectively).
Table 10. Energy expenditure estimate from the criterion and energy intake estimates from diet history and 7-day food diary methods using different statistical analysis in women with COPD (N=19).

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Difference of the means ± SD&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Pearson’s correlation</th>
<th>Intraclass correlations coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>kJd⁻¹</td>
<td>kJd⁻¹</td>
<td>P-values</td>
<td>r</td>
</tr>
<tr>
<td>TEE&lt;sub&gt;DLW&lt;/sub&gt; (Criterion)</td>
<td>7967 ± 1090</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EI&lt;sub_DH&lt;/sub&gt;</td>
<td>5725 ± 766</td>
<td>2242 ± 1362</td>
<td>&lt; 0.001</td>
<td>-0.05</td>
</tr>
<tr>
<td>EI&lt;sub_FD&lt;/sub&gt;</td>
<td>6395 ± 1643</td>
<td>1569 ± 1795</td>
<td>0.001</td>
<td>0.19</td>
</tr>
</tbody>
</table>

<sup>a</sup> criterion – test method.

ICC, intraclass correlation coefficient; TEE<sub>DLW</sub>, total energy expenditure measured by doubly labeled water; EI<sub_DH</sub>, energy intake assessed by diet history interview; EI<sub_FD</sub>, energy intake assessed by 7-day food diary.
Figure 4. Bland-Altman plots showing the difference against the mean of daily energy intake measured by (A) diet history (EI\textsubscript{DH}), (B) 7-day food diary (EI\textsubscript{FD}), and the total daily energy expenditure measured doubly labeled water method (TEE\textsubscript{DLW}) in 19 women with chronic obstructive pulmonary disease.
Results

**Paper III (Energy requirement)**

Pedometer data was collected from 19 patients. One woman did not wear the pedometer as instructed and the pedometer protocols were not filled correctly. Therefore, one woman was excluded from the data analysis. The average number of steps±SD taken daily was 3757±2065 (minimum–maximum: 1530–8310). Estimated PAL from the pedometer was lower by 13.6% than the measured criterion PAL (Table 11). The correlation between the predicted and the measured PAL was significant, and the ICC was low and nonsignificant (Table 11).

Measured and predicted RMRs are presented in Table 11. Five of six prediction equations overestimated RMR between 6.2% and 22.8% compared to the measured RMR by IC. The ICC between indirect calorimetry and prediction equations were moderate for five RMR equations (Table 11).

There was a large variation in the measured and predicted energy requirement. Compared to the criterion method, underestimation of energy requirement was 6.2% by Harris–Benedict, 6.7% by Schofield, 4.6% by WHO, 7.6% by NNR, and 21.3% as assessed by Nordenson, and by Moore, the energy requirement was overestimated by 6.8%. The predicted energy requirement correlated significantly with the criterion DLW method for all six RMR equations (Table 11). The ICC values were ≥ 0.70 in four of six predicted TEE methods (Table 11). In the Bland–Altman plots, the values were more evenly distributed around the mean difference for TEE assessed by Schofield, WHO, Moore, and NNR (Figure 5B–E), whereas the Harris-Benedict and Nordenson estimates exhibited a systematic bias (Figure 5A,F).

The percentage of patients whose predicted individual energy requirement was within ±10% of measured TEE varied among the methods evaluated. For WHO method, 67% of women were within ±10% of measured TEE. For Harris–Benedict, Moore, and NNR, 50% of women were within ±10% of the individually measured TEE, and for Schofield and Nordenson, 56% and 22% of women, respectively, were within ±10% of measured TEE with the DLW method.
Table 11. Estimates of energy expenditure and physical activity level assessed by the criterion and test methods using different statistical analysis in women with COPD (N=19).

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Difference of the means ± SD</th>
<th>Pearson’s correlation</th>
<th>Intraclass correlations coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>kJ d⁻¹</td>
<td>kJ d⁻¹</td>
<td>P-values</td>
<td>ICC</td>
</tr>
<tr>
<td><strong>Resting Metabolic Rate</strong>, kJ d⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Calorimetry (IC)</td>
<td>4832 ± 548</td>
<td>-379 ± 504</td>
<td>0.005</td>
<td>0.53</td>
</tr>
<tr>
<td>Harris-Benedict</td>
<td>5210 ± 480</td>
<td>-358 ± 510</td>
<td>0.009</td>
<td>0.46</td>
</tr>
<tr>
<td>Schofield</td>
<td>5189 ± 407</td>
<td>-471 ± 533</td>
<td>0.002</td>
<td>0.46</td>
</tr>
<tr>
<td>WHO</td>
<td>5302 ± 470</td>
<td>-299 ± 511</td>
<td>0.024</td>
<td>0.53</td>
</tr>
<tr>
<td>NNR</td>
<td>5131 ± 504</td>
<td>-1102 ± 617</td>
<td>&lt; 0.001</td>
<td>0.46</td>
</tr>
<tr>
<td>Moore</td>
<td>5934 ± 632</td>
<td>462 ± 483</td>
<td>0.001</td>
<td>0.49</td>
</tr>
<tr>
<td>Nordensson</td>
<td>4370 ± 349</td>
<td>376 ± 933</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Physical activity level (PAL) |                    |                              |                       |           |                         |
| Criterion (TEE<sub>DLW</sub>/RMR<sub>IC</sub>) | 1.69 ± 0.147 | 0.23 ± 0.145 | < 0.001 | 0.47 | 0.046 | 0.34 - 0.23 - 0.72 |
| Pedometer-determined (PAL<sub>PED</sub>) | 1.46 ± 0.134 | 0.49 | 0.038 | 0.46 - 0.22 - 0.79 |

| Total energy expenditure, kJ d⁻¹ |                    |                              |                       |           |                         |
| Doubly labeled water (DLW) | 8114 ± 907         |                              |                       |           |                         |
| Harris-Benedict x PAL<sub>PED</sub> | 7607 ± 1222 | 507 ± 973 | 0.040 | 0.62 | 0.006 | 0.70 0.23 - 0.89 |
| Schofield x PAL<sub>PED</sub> | 7571 ± 1097 | 543 ± 876 | 0.018 | 0.63 | 0.005 | 0.71 0.21 - 0.89 |
| WHO x PAL<sub>PED</sub> | 1138 ± 1189 | 376 ± 933 | 0.106 | 0.63 | 0.005 | 0.74 0.33 - 0.90 |
| NNR x PAL<sub>PED</sub> | 7494 ± 1265 | 620 ± 975 | 0.015 | 0.64 | 0.004 | 0.70 0.71 - 0.89 |
| Moore x PAL<sub>PED</sub> | 8664 ± 1496 | -550 ± 1137 | 0.056 | 0.63 | 0.005 | 0.69 0.21 - 0.88 |
| Nordensson x PAL<sub>PED</sub> | 6387 ± 1047 | 1727 ± 864 | < 0.001 | 0.62 | 0.006 | 0.40 - 0.19 - 0.77 |

<sup>a</sup> criterion – test method.

ICC, intraclass correlation coefficient; CI, confidence interval; WHO, World Health Organization; NNR, Nordic Nutrition Recommendations
Figure 5. Bland-Altman plots showing the differences in the mean TEE between the DLW method (DLW) and predicted energy requirement by (A) the Harris-Benedict RMR equation (H-B) multiplied by pedometer-determined PAL (PAL_{Ped}), (B) the Schofield RMR equation (SCHOF) multiplied by PAL_{Ped}, (C) the WHO RMR equation (WHO) multiplied by PAL_{Ped}, (D) The MOORE RMR equation (MOORE) multiplied by PAL_{Ped}, (E) the NNR RMR equation (NNR) multiplied by PAL_{Ped}, and (F) the Nordenson RMR equation (NORD) multiplied by PAL_{Ped} in 18 women with COPD.
Paper IV (energy requirement)

Patient characteristics

The patient characteristics are shown in Table 12. Of the 44 patients 34 (77 %) were women. The proportion of patients with GOLD 2, 3 and 4 in women was 32 %, 52 %, and 16 % respectively, and in men, 50 % had GOLD 3 and 50 % GOLD 4 (P = 0.013). The mean BMI and FFMI were low compared to reference values. Fifty % of the patients had BMI and FFMI less than the reference values, and 5 % had normal BMI and FFMI. The RMR, TEE, AEE and PAL varied among the patients (Table 12).

The RMR and TEE had a significant association with FFM (r = 0.820, P < 0.001 respectively r = 0.706, P < 0.001), and FFMI (r = 0.687, P < 0.001 respectively r = 0.673, P < 0.001). BMI was significantly correlated to FEV₁ % predicted (Figure 6). The calculated RMR, TEE and AEE per kg BW and kg FFMI is shown in Table 12. There was a large variation in RMR, TEE, and AEE per kg BW, and per kg FFMI.

Energy expenditure stratified by gender

Table 13 shows patient characteristics and energy expenditure stratified by gender. In the present analysis, the women had higher FEV₁ % predicted and BMI than men (P < 0.001 respectively P = 0.001), and lower FFMI (P < 0.001). Compared to men, women had a lower RMR and TEE per kg BW per day (P < 0.001 respectively P = 0.002), and higher RMR and TEE per kg FFMI per day (P = 0.080 respectively P = 0.005. Percent of FFMI (mean ± SD) was 64 ± 9.3 % in women, and 87 ± 5.7 % in men, and this difference was associated with male sex (β = 23.4; 95 % CI, 17.1 to 29.7; P < 0.001).

Energy expenditure stratified by disease severity

BMI in this study decreased significantly with increase in disease severity (P < 0.001) (Table 13). Patients with GOLD 2 had a lower RMR per kg BW per day than patients with GOLD 3 and GOLD 4 (P = 0.020 respectively P = 0.002). TEE per kg FFMI per day was higher in patients with GOLD 2 than patients with GOLD 3 (P = 0.007), and GOLD 4 (P < 0.001). Comparing by disease severity, the patients with GOLD 2 had significantly lower % of FFMI than with GOLD 3 (P < 0.001), and GOLD 4 (P < 0.001).
Table 12. Patient characteristics, energy expenditure, and physical activity level of women and men with COPD.

<table>
<thead>
<tr>
<th>General characteristics</th>
<th>N</th>
<th>Mean ± SD</th>
<th>Min-Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>44</td>
<td>66.0 ± 7.5</td>
<td>47.0 - 80.0</td>
</tr>
<tr>
<td>FEV1, % predicted value</td>
<td>41</td>
<td>42.6 ± 16.7</td>
<td>19 - 78</td>
</tr>
<tr>
<td>Disease severity, n (%)a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOLD 2, 50% ≤ FEV1 &lt; 80% predicted</td>
<td>10 (24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOLD 3, 30% ≤ FEV1 &lt;50 % predicted</td>
<td>21 (52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOLD 4, &lt; 30% predicted</td>
<td>10 (24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>44</td>
<td>21.4 ± 3.8</td>
<td>13.5 - 30.0</td>
</tr>
<tr>
<td>FFMI, kg/m²</td>
<td>44</td>
<td>14.4 ± 1.7</td>
<td>11.4 - 19.0</td>
</tr>
<tr>
<td>Pack-years</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial pCO₂, kPa</td>
<td>41</td>
<td>5.2 ± 0.56</td>
<td>4.3 - 6.7</td>
</tr>
<tr>
<td>Arterial pO₂, kPa</td>
<td>41</td>
<td>9.7 ± 2.2</td>
<td>4.4 - 18.4</td>
</tr>
<tr>
<td>O₂ saturation</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Energy expenditure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RMR, kJ/day</td>
<td>44</td>
<td>5039 ± 834</td>
<td>3617 - 7464</td>
</tr>
<tr>
<td>TEE, kJ/day</td>
<td>44</td>
<td>7920 ± 1348</td>
<td>5197 - 11075</td>
</tr>
<tr>
<td>AEE, kJ/day</td>
<td>44</td>
<td>2884 ± 847</td>
<td>723 - 4594</td>
</tr>
<tr>
<td>RMR, kJ/kg BW/day</td>
<td>44</td>
<td>89 ± 16.6</td>
<td>62 - 135</td>
</tr>
<tr>
<td>RMR, kJ/kg FFM/day</td>
<td>44</td>
<td>130 ± 15.0</td>
<td>108 - 192</td>
</tr>
<tr>
<td>TEE, kJ/kg BW/day</td>
<td>44</td>
<td>139 ± 22.7</td>
<td>98 - 201</td>
</tr>
<tr>
<td>TEE, kJ/kg FFM/day</td>
<td>44</td>
<td>204 ± 29.6</td>
<td>142 - 318</td>
</tr>
<tr>
<td>AEE, kJ/kg BW/day</td>
<td>44</td>
<td>50 ± 13.4</td>
<td>15 - 75</td>
</tr>
<tr>
<td>AEE, kJ/kg FFM/day</td>
<td>44</td>
<td>75 ± 22.8</td>
<td>22 - 125</td>
</tr>
<tr>
<td>PAL</td>
<td>44</td>
<td>1.58 ± .18</td>
<td>1.15 - 2.09</td>
</tr>
</tbody>
</table>
According to Global Initiative for Chronic Obstructive Lung Disease (GOLD) (3). FEV$_1$, forced expiratory volume in 1 s; GOLD, Global Initiative for Chronic Obstructive Lung Disease; BMI, body mass index; FFMI, fat-free mass index; RMR, resting metabolic rate; TEE, total daily energy expenditure; AEE, activity energy expenditure; BW, body-weight; FFM, fat-free mass; PAL, physical activity level.

Figure 6. Correlation between FEV$_1$ % predicted and (A) BMI, kg/m$^2$, and (B) FFMI, kg/m$^2$. 
Table 13. Patient characteristics, and energy expenditure in patients with COPD stratified by gender and by disease severity.

<table>
<thead>
<tr>
<th></th>
<th>Stratified by gendera</th>
<th>Stratified by disease severitya</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women N = 34</td>
<td>Men N = 10</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>67 ± 7.3</td>
<td>63 ± 7.8</td>
</tr>
<tr>
<td>FEV₁, % predicted valueb</td>
<td>46.6 ± 16.9c</td>
<td>30.4 ± 8.3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.1 ± 3.8</td>
<td>18.7 ± 2.1</td>
</tr>
<tr>
<td>FFMI, kg/m²</td>
<td>13.9 ± 1.3</td>
<td>16.3 ± 1.6</td>
</tr>
<tr>
<td>RMR, kJ/day</td>
<td>4727 ± 526</td>
<td>6087 ± 851</td>
</tr>
<tr>
<td>TEE, kJ/day</td>
<td>7591 ± 1176</td>
<td>9041 ± 1343</td>
</tr>
<tr>
<td>AEE, kJ/day</td>
<td>2864 ± 900</td>
<td>2955 ± 672</td>
</tr>
<tr>
<td>PAL</td>
<td>1.61 ± 0.19</td>
<td>1.49 ± 0.10</td>
</tr>
<tr>
<td>RMR, kJ/kg BW/day</td>
<td>84 ± 14.0</td>
<td>107 ± 12.1</td>
</tr>
<tr>
<td>RMR, kJ/kg FFM/day</td>
<td>132 ± 15.5</td>
<td>123 ± 10.7</td>
</tr>
<tr>
<td></td>
<td>TEE, kJ/kg BW/day</td>
<td>TEE, kJ/kg FFM/day</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td></td>
<td>134 ± 20.9</td>
<td>158 ± 18.3</td>
</tr>
<tr>
<td></td>
<td>158 ± 18.3</td>
<td>134 ± 20.0</td>
</tr>
<tr>
<td></td>
<td>0.002</td>
<td>0.169</td>
</tr>
<tr>
<td></td>
<td>211 ± 29.0</td>
<td>182 ± 19.2</td>
</tr>
<tr>
<td></td>
<td>182 ± 19.2</td>
<td>211 ± 29.0</td>
</tr>
<tr>
<td></td>
<td>0.005</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>50 ± 14.3</td>
<td>52 ± 10.3</td>
</tr>
<tr>
<td></td>
<td>52 ± 10.3</td>
<td>50 ± 14.3</td>
</tr>
<tr>
<td></td>
<td>0.708</td>
<td>0.987</td>
</tr>
<tr>
<td></td>
<td>79 ± 23.3</td>
<td>94 ± 22.3</td>
</tr>
<tr>
<td></td>
<td>59 ± 12.6</td>
<td>79 ± 23.3</td>
</tr>
<tr>
<td></td>
<td>0.015</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Data are represented as mean ± SD; \( b N = 41; \) \( c N = 31 \)

FEV\(_1\), Forced expiratory volume in 1st second; BMI, body mass index; FFMI, fat-free mass; RMR, resting metabolic rate; TEE, total energy expenditure; AEE, activity energy expenditure; PAL, physical activity level; BW, body-weight; FFM, fat-free mass.
Results

Energy expenditure and lung function

The correlation between energy expenditure and FEV\textsubscript{1} % predicted is shown in Figure 7. FEV\textsubscript{1} % predicted had a significant correlation with RMR/kg BW/day ($r = -0.503$, $P = 0.001$), RMR/kg FFM/day ($r = 0.338$, $P = 0.031$), TEE/kg FFM/day ($r = 0.671$, $P < 0.001$), and AEE/kg FFM/day ($r = 0.641$, $P < 0.001$).

Correlates of energy expenditure

Multiple linear regression analysis performed separately revealed that FFM was independently correlated to RMR ($\beta = 82.97$, 95% CI, 49.7 to 116.2, $P < 0.001$), and TEE ($\beta = 164.30$, 95% CI, 113.1 to 215.5, $P < 0.001$) after adjusting for age, gender, and FEV\textsubscript{1} % predicted.

In the separate analysis, RMR and TEE per kg BW per day continued to be significantly lower in women than men ($\beta = 26.45$, 95% CI, 11.5 to 41.4, $P = 0.001$ respectively $\beta = 27.282$, 95% CI, 5.0 to 49.4) after adjustment for age, FEV\textsubscript{1} % predicted and FFM. The increase in age correlated independently with lower TEE per kg BW and per kg FFM per day, AEE per kg BW and per kg FFM per day ($\beta = -0.923$, 95% CI, -1.7 to -0.13, $P = 0.025$, $\beta = -1.094$, 95% CI, -2.0 to -0.19, $P = 0.020$, $\beta = -0.745$, 95% CI, -1.3 to -2.3, $P = 0.040$, respectively $\beta = -0.913$, 95% CI, -1.7 to -0.18, $P = 0.022$). FEV\textsubscript{1} % predicted had an independent negative association with RMR per kg BW per day ($\beta = -1.209$, 95% CI, -2.1 to -0.28, $P = 0.041$), and correlated positively with TEE per kg FFM per day ($\beta = 1.154$, 95% CI, 0.70 to 1.6, $P < 0.001$), after adjusting for age, gender and FFM.
Figure 7. Correlation between $FEV_1$ % predicted and (A) RMR, kJ/kg BW/day; (B) RMR, kJ/kg FFM/day; (C) TEE, kJ/kg BW/day; (D) TEE, kJ/kg FFM/day; (E) AEE, kJ/kg BW/day; (F) AEE, kJ/kg FFM/day.
Paper V (OLIN BMI study)

BMI and clinical characteristics

The characteristics of the 635 subjects with COPD and 991 subjects without COPD are shown in Table 14. The proportion of COPD subjects with GOLD 1, GOLD 2 and GOLD 3-4 was, 41.1 %, 51.2 % and 7.7 %, respectively. The mean BMI in COPD subjects was significantly lower than the non-COPD (P < 0.001), NLF (P = 0.004) and RSP group (P < 0.001).Significantly more COPD subjects were under-weight than the non-COPD, NLF and RSP subjects (P = 0.001; P = 0.010; P = 0.001, respectively). Fewer COPD subjects were obese than non-COPD, NLF and RSP group (P = .001; P = .038; P <.001, respectively). Subjects with GOLD 1 had significantly fewer mean pack-years than those with GOLD 2 (12.3 vs 17.8; P < 0.001) and with GOLD 3-4 (12.3 vs 26; P < 0.001). A higher proportion of GOLD 2 subjects were current smokers than the subjects with GOLD 1 (39 % vs 28 %, P = 0.001), or GOLD 3-4 (39% vs 29%, P = 0.002).

Multivariate linear regression analysis revealed an independent association between COPD and BMI after adjusting for age, gender, pack-years and current smoking status when compared to non-COPD (β = -0.99; 95% CI, -1.44 to -0.55; P < 0.001), NLF (β = -0.645; 95% CI, -1.1 to -0.19; P = 0.005), and RSP group (β = -2.2; 95% CI, -2.9 to –1.5; P < 0.001). The number of pack-years and current smoking status had an independent association with BMI when subjects with COPD were compared to non-COPD (β = 0.020; 95% CI, 0.001 to 0.040; P = .040 respectively β = -0.46; 95% CI, -0.811 to -0.101; P = 0.012), and NLF subjects (β = 0.024; 95% CI, 0.004 to 0.044; P = 0.017 respectively β = -0.53; 95% CI, -0.891 to -0.166; P = 0.004). Comparing the subjects with COPD and RSP, current smoking status was independently associated with BMI (β = -0.652; 95% CI, -1.127 to -0.178; P = 0.007).

Comparison of subjects with COPD by GOLD grading and NLF

The prevalence of being under-weight was highest among women with GOLD 3-4 and lowest in those with NLF (33.3 % vs 14.8 %; P = 0.022) (Figure 8A). Men with GOLD 3-4 had the highest and those with NLF had the lowest prevalence of being under-weight (28.6 % vs 7.4 %; P < 0.001) (Figure 8B).
Comparison of women and men with COPD and NLF

Women with COPD had lower mean BMI (25.9 kg/m$^2$ vs 26.7 kg/m$^2$, $P = 0.015$) and a higher proportion were under-weight than men with COPD (22% vs 11%, $P < 0.001$). Fifty-one percent of men with COPD were over-weight compared to 37% in women with COPD ($P < 0.001$). Compared to COPD men, women with COPD had fewer pack-years of smoking (14yrs. vs 18 yrs., $P = 0.015$), whereas more women were current smokers (38% vs 30%, $P = 0.042$). In the NLF group, significantly more women with NLF were in the under-weight group (15% vs 7%, $P = 0.001$), and had fewer pack-years of smoking than men (5 yrs. Vs 8 yrs., $P < 0.001$).

The women with COPD compared to NLF women had a lower BMI (25.9 kg/m$^2$ vs 27.1 kg/m$^2$, $P = 0.001$), higher prevalence of being under-weight (22% vs 15%, $P = .022$), more pack-years of smoking (14 yrs. Vs 5 yrs., $P <0.001$), and more were current smokers (38% vs 14%, $P < 0.001$). Men with COPD had more pack-years of smoking (18 yrs. Vs 8 yrs., $P < 0.001$), and more were current smokers (30% vs 12%, $P < 0.001$) than NLF men.

Comparison of BMI categories in women and men with COPD

Women

The comparison between different BMI categories in women with COPD with regard to their clinical characteristics are presented in Table 15. Prevalence of clinically relevant dyspnea (mMRC ≥ 2) was significantly higher in obese women compared to the other BMI groups, (all $Ps < 0.005$). Oxygen saturation at rest (%) was significantly lower in over-weight women in comparison to the under-weight ($P = 0.018$) and normal-weight women with COPD ($P = 0.010$). Less obese women were current smokers than under-weight or over-weight women ($P = 0.045$).

Men

Under-weight men had significantly lower FEV$_1$ % predicted than normal-weight men ($P = 0.019$) (Table 15). Compared to the men in the normal-weight group the rate of clinically significant dyspnea was higher in under-weight, over-weight, and in obese men (all $P$-values < 0.005). The proportion of current smokers was lower in over-weight than in the low-weight men ($P = 0.040$) (Table 15).
Table 1. Clinical characteristics of the study population by spirometry classification; COPD and non-COPD, non-COPD further divided into Normal Lung Function and Restrictive Spirometry Pattern.

<table>
<thead>
<tr>
<th></th>
<th>COPD</th>
<th>Non-COPD</th>
<th>P1</th>
<th>NLF</th>
<th>P2</th>
<th>RSP</th>
<th>P3</th>
<th>P4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Age, yrs.</td>
<td>635</td>
<td>991</td>
<td>0.004</td>
<td>64.6 ± 11.3</td>
<td>&lt;0.0015</td>
<td>68.8 ± 10.0</td>
<td>0.128</td>
<td>&lt;0.0015</td>
</tr>
<tr>
<td>Gender, women, n (%)</td>
<td></td>
<td></td>
<td>0.066</td>
<td>378 (51.9)</td>
<td>0.125</td>
<td>92 (44.9)</td>
<td>0.627</td>
<td>0.443</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.4 ± 4.1</td>
<td>27.4 ± 4.3</td>
<td>&lt;0.001</td>
<td>27.0 ± 4.0</td>
<td>0.0145</td>
<td>28.8 ± 4.8</td>
<td>&lt;0.0015</td>
<td>&lt;0.0015</td>
</tr>
<tr>
<td>BMI categories, n (%)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under-weight, BMI &lt; 22.5 kg/m²</td>
<td>99 (15.6)</td>
<td>99 (10.0)</td>
<td>0.001</td>
<td>86 (10.9)</td>
<td>0.010</td>
<td>13 (6.3)</td>
<td>0.001</td>
<td>0.050</td>
</tr>
<tr>
<td>Normal-weight, BMI 22.5 - &lt; 25 kg/m²</td>
<td>146 (23.0)</td>
<td>210 (21.2)</td>
<td>0.391</td>
<td>184 (23.4)</td>
<td>0.853</td>
<td>26 (12.7)</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Over-weight, BMI 25 - &lt; 30 kg/m²</td>
<td>285 (44.9)</td>
<td>452 (45.6)</td>
<td>0.773</td>
<td>352 (44.8)</td>
<td>0.970</td>
<td>100 (48.8)</td>
<td>0.330</td>
<td>0.307</td>
</tr>
<tr>
<td>Obese, BMI ≥ 30 kg/m²</td>
<td>105 (16.5)</td>
<td>230 (23.2)</td>
<td>0.001</td>
<td>164 (20.9)</td>
<td>0.038</td>
<td>66 (32.2)</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>75.5 ± 16.5</td>
<td>93.5 ± 13.4</td>
<td>&lt;0.001</td>
<td>97.9 ± 10.8</td>
<td>&lt;0.0013</td>
<td>76.6 ± 7.6</td>
<td>0.364</td>
<td>&lt;0.0013</td>
</tr>
<tr>
<td>mMRC ≥ 2, n (%)</td>
<td>83 (13.6)</td>
<td>49 (5.1)</td>
<td>0.035</td>
<td>25 (3.3)</td>
<td>&lt;0.0015</td>
<td>24 (12.4)</td>
<td>0.063</td>
<td>&lt;0.0015</td>
</tr>
<tr>
<td>O₂ saturation at rest, %</td>
<td>96.3 ± 2.2</td>
<td>97.1 ± 1.4</td>
<td>&lt;0.001</td>
<td>97.2 ± 1.3</td>
<td>&lt;0.0015</td>
<td>96.7 ± 1.4</td>
<td>0.0093</td>
<td>0.0015</td>
</tr>
<tr>
<td>Pack-years</td>
<td>16.2 ± 16.1</td>
<td>7.2 ± 11.2</td>
<td>&lt;0.001</td>
<td>6.9 ± 10.6</td>
<td>&lt;0.0015</td>
<td>8.4 ± 12.9</td>
<td>&lt;0.0015</td>
<td>0.094</td>
</tr>
<tr>
<td>Smoking habits, n (%)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>160 (25.2)</td>
<td>468 (47.3)</td>
<td>372 (47.4)</td>
<td>96 (46.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>261 (41.2)</td>
<td>400 (40.4)</td>
<td>313 (39.9)</td>
<td>87 (42.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>213 (33.6)</td>
<td>122 (12.3)</td>
<td>&lt;0.001</td>
<td>100 (12.7)</td>
<td>&lt;0.001</td>
<td>22 (10.7)</td>
<td>&lt;0.001</td>
<td>0.260</td>
</tr>
</tbody>
</table>
Data are represented as mean ± SD, until stated otherwise; ¹ P-value comparing COPD and non-COPD; ² P-value comparing COPD and normal lung function controls; ³ P-value comparing COPD and restrictive spirometry pattern; ⁴ P-value comparing normal lung function and restrictive spirometry pattern; ⁵ significant also after Bonferroni correction when comparing COPD to normal and restrictive lung function subjects respectively; ᵇ data collected for ₙ = 609; ᶜ data collected for ₙ = 954; ᵈ data collected for ₙ = 760; ᵉ data collected for ₙ = 194. NLF, Normal Lung Function; RSP, Restrictive Spirometry Pattern; FEV₁, Forced expiratory volume in 1st second; mMRC, modified Medical Research Council dyspnea scale.
Figure 8. Prevalence of different BMI categories in (A) women with normal lung function, GOLD 1, GOLD 2, and GOLD 3-4, and (B) men with normal lung function, GOLD 1, GOLD 2, and GOLD 3-4.
**Results**

*BMI in relation to FEV₁ % predicted in subjects with COPD*

In women with under-weight, FEV₁ % predicted increased with an increase in BMI (P = 0.048) (Figure 9A) and this difference remained significant after adjusting for smoking status (P = 0.048). A similar trend was observed in the under-weight men, but it did not achieve statistical significance (Figure 9A). In other BMI categories no relation between BMI and FEV₁ % predicted was found (Figure 9B-9D).
Table 15. Comparison of clinical characteristics stratified by BMI in women and in men with COPD.

<table>
<thead>
<tr>
<th></th>
<th>Women, N (%)</th>
<th>Men, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Under-weight, BMI &lt; 22.5 kg/m²</td>
<td>Normal-weight, BMI 22.5 - &lt;25 kg/m²</td>
</tr>
<tr>
<td><strong>Age, yrs.</strong></td>
<td>59 (21.8)</td>
<td>66 (24.4)</td>
</tr>
<tr>
<td><strong>FEV₁, % predicted</strong></td>
<td>66.0 ± 12.5</td>
<td>66.9 ± 10.3</td>
</tr>
<tr>
<td><strong>mMRC ≥ 2, n (%)</strong></td>
<td>5 (9.3)</td>
<td>8 (12.3)</td>
</tr>
<tr>
<td><strong>O₂ saturation at rest, %</strong></td>
<td>96.9 ± 1.5</td>
<td>96.9 ± 1.7</td>
</tr>
<tr>
<td><strong>Pack-years</strong></td>
<td>16.0 ± 15.4</td>
<td>15.5 ± 14.8</td>
</tr>
<tr>
<td><strong>Smoking habits, n (%)</strong></td>
<td>18 (30.5)</td>
<td>16 (24.2)</td>
</tr>
<tr>
<td><strong>Non-smoker</strong></td>
<td>12 (20.3)</td>
<td>21 (31.8)</td>
</tr>
<tr>
<td><strong>Current smoker</strong></td>
<td>29 (49.2)</td>
<td>29 (43.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>P₁</th>
<th>P₂</th>
<th>P₃</th>
<th>P₄</th>
<th>P₅</th>
<th>P₆</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yrs.</strong></td>
<td>0.956</td>
<td>1.00</td>
<td>0.770</td>
<td>1.00</td>
<td>0.335</td>
<td>0.023</td>
</tr>
<tr>
<td><strong>FEV₁, % predicted</strong></td>
<td>0.018</td>
<td>0.175</td>
<td>0.004</td>
<td>0.040</td>
<td>0.040</td>
<td>0.040</td>
</tr>
<tr>
<td><strong>mMRC ≥ 2, n (%)</strong></td>
<td>0.770</td>
<td>1.00</td>
<td>0.004</td>
<td>0.040</td>
<td>0.040</td>
<td>0.040</td>
</tr>
<tr>
<td><strong>O₂ saturation at rest, %</strong></td>
<td>0.018</td>
<td>0.175</td>
<td>0.004</td>
<td>0.040</td>
<td>0.040</td>
<td>0.040</td>
</tr>
<tr>
<td><strong>Pack-years</strong></td>
<td>0.335</td>
<td>0.147</td>
<td>0.921</td>
<td>0.318</td>
<td>0.45</td>
<td>0.388</td>
</tr>
</tbody>
</table>

**Underweight**, BMI < 22.5 kg/m²; **Normal-weight**, BMI 22.5 - <25 kg/m²; **Over-weight**, BMI 25 - <30 kg/m²; **Obese**, BMI ≥ 30 kg/m². P-values from t-tests or Fisher's Exact Tests.
Data are represented as mean ± SD, until stated otherwise; ¹ p-value comparing low-weight and normal-weight women respectively men with COPD; ² p-value comparing low-weight and over-weight women respectively men with COPD; ³ p-value comparing low-weight and obese women respectively men with COPD; ⁴ p-value comparing normal-weight and over-weight women respectively men with COPD; ⁵ p-value comparing normal-weight and obese women respectively men with COPD; ⁶ p-value comparing over-weight and obese women respectively men with COPD; ⁷ data collected for n = 36; ⁸ data collected for n = 76; ⁹ data collected for n = 184; ¹⁰ data collected for n = 57.

FEV₁, Forced expiratory volume in 1st second; mMRC, modified Medical Research Council dyspnea scale.
Figure 9. Correlation between BMI and FEV\textsubscript{1} % predicted in women and men with COPD having (A) BMI $< 22.5$ kg/m\textsuperscript{2}, (B) BMI $= 22.5$ - $24.9$ kg/m\textsuperscript{2}, (B) BMI $= 25$ - $29.9$ kg/m\textsuperscript{2}, and (D) BMI $\geq 30$ kg/m\textsuperscript{2}.
Discussion

A substantial number of patients with COPD experience an involuntary loss of body-weight which is related to increased morbidity and mortality. To maintain an energy balance, in this group of patients, it is essential to accurately quantify each patient’s daily energy expenditure (TEE), energy intake, and energy requirements. We have conducted studies in which methods assessing TEE, energy intake and energy requirements were validated.

The results of the validation study (paper I-III) show that in free-living women with COPD the total daily energy expenditure can be assessed with good accuracy using SenseWear Armband (SWA) with software version 5.1. However, the other version of SWA namely, SWA 6.1 and ActiHeart methods both tended to underestimate total daily energy expenditure. The activity energy expenditure was underestimated when assessed by both SWA and ActiHeart in the investigated group of patients. The energy intake assessed by diet history and 7-day food diaries was also underestimated when compared with the criterion method, doubly labeled water (DLW). A higher proportion of women with COPD were identified as valid reporters when energy intake was assessed by 7-day food diary compared with diet history (63% vs 32%, respectively). The predicted energy requirement assessed by pedometer-determined physical activity level and six commonly used RMR equations correlated significantly, and five of these six equations had a significant agreement with the criterion method, DLW, in this group of women with COPD. The predicted energy requirement by WHO equation multiplied by pedometer-determined PAL gave better estimates at both group and individual levels than other validated equations.

In paper IV there was a considerable individual variation in RMR, TEE, activity energy expenditure and physical activity level. However, we believe that the presented data of energy expenditure per kg body-weight and per kg fat-free mass measured by the Gold Standard DLW method in patients with COPD may be applied for calculation of energy requirement in this group of patients. BMI correlated significantly with FEV1 % predicted values. An increase in energy expenditure was indicated as lung function worsened in the investigated group.

In the population-based study (paper V), the results revealed that COPD subjects had significantly lower BMI and a higher proportion with underweight compared to non-COPD, and its sub-groups namely, normal lung function, and restrictive spirometry pattern subjects. This association
between COPD and lower BMI was not altered when adjustments were made for age, gender, pack-years and current smoking status. COPD subjects had more pack-years of smoking and a higher proportion of current smokers than non-COPD, normal lung function and restrictive spirometry pattern subjects. The percentage of obese subjects was significantly lower in the COPD group than the other groups. Furthermore, we found that women with COPD had significantly lower BMI and a higher prevalence of being underweight than men with COPD.

**Discussion of methods**

**Paper I (Energy expenditure)**

The doubly labeled water method was used as a criterion method for measuring TEE since it is considered to be the “Gold Standard”, and has been shown to be accurate to 1% with a 2% to 8% coefficient of variation depending on isotope dose and length of the elimination period (135). The DLW method measures the habitual TEE in free-living subjects and provides a cumulative estimate of TEE over a period, usually between 7- and 20-days (136). The isotopes used are non-radioactive and therefore safe to be used in humans, even in pregnancy, infancy and the elderly. It is easy and simple both to administer and to collect and store the urine samples for analysis. The day-to-day changes in TEE are not provided (136). The high cost of DLW and analytical equipment and significant technical expertise required for the analysis complicate and limit its use in daily clinical settings.

In recent years many different motion sensors have been developed and used to assess physical activity and energy expenditure in different populations including patients with COPD (110,137-145). In studies concerning patients with COPD, the aim has often been to assess the physical activity (39,100,102,108,138), however studies assessing TEE using motion sensors are few (102,106,143). The SWA is one of the commonly used motion sensor in different populations (138-142), and has been shown to assess TEE reliably in other groups (139-142). In patients with COPD, the SWA has primarily been utilized for assessment of physical activity (100-102,105,108). However, studies, concerning assessment of TEE using SWA in patients with COPD are scarce, and to date, and to our knowledge, our study was the first to validate SWAs ability to assess TEE exclusively in women with COPD. The SWA has been designed to collect and analyze a broad range of data from the body and its movement allowing to quantify physical activity and energy expenditure more accurately on a daily basis (146). The combination of heat sensors and biaxial accelerometer allows the armband to detect the increased effort and energy expenditure associated with load carrying, to measure all
forms of physical activity including the upper and lower body movements, and non-ambulatory physical activity. The SWA is a small, user-friendly, non-costly and simple to administer, and no preparation or training prior to long-term registration is required. It does not interfere with the daily activities of life and can be worn throughout the day except during water activities. Besides TEE and physical activity, it assesses activity energy expenditure, rest and sleeping time. Among the few limitations of using SWA are; 1) it cannot be worn during water activities, hence energy expenditure during such activities is not determined; 2) SWA does not estimate RMR and diet induced thermogenesis.

Another motion sensor that has been used for assessment of TEE and physical activity in different populations is ActiHeart (110,145-149). To our knowledge, to date, TEE has not been estimated by using ActiHeart in the studies of patients with COPD. The ActiHeart is a compact, device that integrates a heart rate recorder and an accelerometer, which can be worn throughout the day and is waterproof. The daily estimates derived from ActiHeart are TEE, RMR, activity energy expenditure, diet induced thermogenesis, and physical activity level. To validate a motion sensor (ActiHeart) that combines a heart rate recorder and accelerometer seemed both logical and attractive way of assessment of TEE since patients with COPD may often have high resting heart rates (150). The ActiHeart is a light, small, user-friendly, and non-costly device. The limitations of this device are that it is worn on ECG pads which may cause skin irritation if used for longer periods. To synchronize the ActiHeart individually, an 8-minute step test is required. The step test starts at a lower speed and increases with time and can be quite demanding especially in patients with COPD.

The study patients experienced both the SWA and ActiHeart as user friendly. No reports were received related to technical problems for these monitors. Several participants reported being more comfortable with the SWA, and others preferred the ActiHeart. However, the patients in our study reported that they found the step test to be very demanding, and they were not able to complete the entire test.

**Paper II (Energy intake)**

The methods chosen to assess self-reported energy intake were both retrospective and prospective methods, namely, diet history interview respectively 7-day food diary. We used diet history interview aimed to capture the habitual energy intake. Diet history interviews may reflect the studied subject’s habitual energy intake, but this method has some limitations that are associated with recall (memory), seasonality, and its
ability to identify individual differences in energy intake (112,114,135). The 7-day food diary aims to reflect the energy intake of the period during which food and fluid intake is recorded, and thus the issues related to the memory are eliminated. This type of method has often been considered the most accurate and precise method of dietary assessment (112). However, poor compliance can be an issue sometimes with this method, e.g. recording of food intake over several days can be seen as tedious and time consuming, and an alteration of the diet during the recording period might occur (112).

**Paper III & IV (Energy requirement)**

In order to calculate energy requirement in women with COPD, four commonly used and two disease-specific RMR equations were used along with the physical activity level determined by a pedometer SW-200. Calculating energy requirement from RMR equations is feasible, widely available, simple, and does not require any particular instrument. However, four commonly used equations are based on healthy subjects from different time periods (90-93), and one of the disease-specific RMR equation requires measuring FFM (95). When using the common RMR equations, substantial variation in RMR, TEE, and consequently the energy requirement need to be considered.

The pedometer SW-200 has been widely used in different studies and shown to be valid (116,117,151-153). To our knowledge, this is the first study using pedometer-determined physical activity level for the calculation of energy requirement in women with COPD. The limitations of the pedometer are that steps taken with a lower force than 0.35 g are not registered, and the upper body movements are not captured by the pedometer. Nonetheless, using an individualized physical activity level value may give a better estimate than using a theoretical physical activity level value.

All studies on TEE as measured by DLW in patients with COPD were systematically identified, and the data from three studies were acquired and analyzed further (87,88,124). As mentioned earlier, the DLW method is “Gold Standard” for measuring TEE. By analyzing together the data from these studies, our aim was to provide valid and valuable results for the calculation of energy requirement in COPD patients. Nevertheless, more studies with larger number of COPD patients are desirable for measuring TEE by DLW method.
**Paper V (BMI OLIN study)**

In this population-based OLIN study, structured interview questionnaire was used to gather the data on respiratory diseases and symptoms, co-morbidities, medication and smoking habit. The questions regarding respiratory symptoms are validated (126-128). This questionnaire has been used in OLIN studies since 30 years. The structured interview is suitable for population-based studies, since most of the data can be collected regardless of the subject arrives for the examination or not.

**Discussion of main results**

**Strengths and limitations**

The studies included in this thesis have both strengths and limitations. In the validation study (Papers I-III), the strengths are: 1) this study is the first to assess TEE, energy intake and energy requirement exclusively in women with COPD; 2) the DLW method, which is a Gold Standard for determining TEE, was used as the criterion method; 3) we also validated the utility of the SWA and ActiHeart monitor in assessments of TEE and activity energy expenditure, which had not been previously established in women with COPD; 4) the physical activity level values were determined from a pedometer, which has not been previously done. The limitations are: 1) the patients with very severe COPD were not included. The reason for not including this group of patients was that the study patients´ required to conduct many different tasks. These tasks may have been perceived as cumbersome by this group of patients since they are a fragile group with many symptoms. Nevertheless, women with moderate and severe COPD were included; 2) in Paper III we did not test the ability of the pedometer to register steps at different speeds prior to collection of data. The study patients had to perform number of tasks that took 5-6 hours, and to put more burden on them seemed inappropriate. However, collecting pedometer data for at least 12 days for each patient resulted in covering the natural variation in day to day activity. In Paper IV, among the strengths are that, besides measuring RMR and TEE with Gold Standard methods, the analysis of the DLW was conducted in the same laboratory in all the three original studies. A limitation is that different devices were used for measuring pulmonary function, and body composition, which may have affected the outcome. Furthermore, the distribution of gender across the range of COPD severity was not uniform. The difference in devices used and in distribution of gender was due to the heterogeneity of the studies that were reviewed and evaluated in Paper IV.
Among the strengths of the population-based study (paper V) are; 1) large COPD cohort with a distribution of disease severity comparable to what has been shown in other population-based studies (154); 2) spirometry criteria for COPD were based on post-bronchodilator spirometry; 3) validated questionnaire was used. There is an obvious benefit of using questionnaires that have been validated throughout the many projects in the OLIN study over 30 years; 4) the lung function tests and interview were performed by well trained and experienced personnel, and the same personnel did all spirometry tests. The possible limitation is the absence of body composition measurement, that may have provided more valuable information regarding the fat-free mass, and fat-mass. Research in last 5-10 years suggests that fat-free mass is a better measure with regards to mortality and fat-mass is more relevant to metabolic disease such as cardiovascular disease (155). Nevertheless, at present BMI is used in epidemiological research, since it is a reliable, more practical and feasible measure of nutritional status (52,58-60).

**Paper I (Energy expenditure)**

Information on measured energy expenditure by DLW method in patients with COPD has been scarce (66, 87,88), especially from women with COPD. Using the DLW method for measuring TEE is costly, and needs specific technical expertise, thus its usage in clinics and research is very limited. Different motion sensors have been used to assess mainly physical activity and also TEE in patients with COPD (102,105-108,137,156). However, to our knowledge, none of the motion sensors had been validated for assessment of TEE in free-living patients with COPD prior to our study.

We have validated the utility of the SWA using software version 5.1 and 6.1, and ActiHeart monitors in the assessment of TEE and activity energy expenditure in free-living women with COPD. The SWA has been used in many studies in patients with COPD, primarily to estimate activity energy expenditure in a free-living state (100-102,108,137,156), however, for TEE estimation, SWA has been utilized in laboratory settings only (106,107,109,138). We have shown in our study that the TEE can reliably be assessed with SWA version 5.1, whereas version 6.1 underestimated TEE by approximately 9%. Based on these results, further analyses showed that at least four days of measurement are required to reliably assess TEE with SWA version 5.1. Although our study was conducted in patients with COPD, the results are consistent as well with reports that have validated SWA for assessment of TEE in other adult populations in the free-living state (139-141). The software versions of SWA used in the aforementioned studies were different. St-Onge et al. (139) analyzed their data using version 4.02,
Johannsen et al. (140) used 6.1, and as in our study, Mackey et al. (141) analyzed data using both 5.1 and 6.1 versions. They (Mackey et al.) reported that version 5.1 performed better than version 6.1, a finding very similar to ours. Another study conducted in children also indicated that version 5.1 gave better estimates of TEE than 6.1 (142). Thus, it may be important to choose a reliable software version when using SWA for estimation of TEE. The results of the present study are in conformity even with the studies that have validated SWA for estimation of TEE in laboratory settings using criterion methods other than DLW (106,107,109, 157). Hill et al. has shown that the estimations of TEE from SWA are sensitive to small but important changes (109). A systematic review of the validity of activity monitors has shown varying results from the field and laboratory studies (158). This heterogeneity could partly be explained by the type of activity monitor used. Nevertheless, our results were consistent with studies conducted both in a free-living state (139-141) and in laboratory settings (106,107,109,138), which can partly be because of the similar motion sensor (SWA) used in these studies.

The estimates of TEE using ActiHeart were lower by approximately 9% and the agreement was substantial when compared to criterion method, DLW. The present analyses were based on the manufacturer’s algorithms in contrast to other studies conducted in children and adolescents, which have used modified multivariate regression models (148,149). In a recent validation study of ActiHeart in young adults, the performance of this device varied across the activities performed (159).

Although SWA 5.1 seemed to assess activity energy expenditure more accurately than SWA 6.1 and ActiHeart, all methods underestimated activity energy expenditure compared to criterion method. The SWA does not provide RMR assessment; therefore, we calculated activity energy expenditure from TEE using SWA and RMR calculated from Harris-Benedict equation for women (90,141). Using Harris-Benedict RMR equation may have influenced the activity energy expenditure assessment using SWA. The ActiHeart provides the estimates of activity energy expenditure and these were used in the validation analyses. The ActiHeart requires an 8-minute step test to synchronize the monitor at an individual level before the long-term registration. None of the patients in our study were able to complete the step-test, and this might have influenced the outcome.

The motion sensors are considered to be more accurate in assessing physical activity and TEE than accelerometers. However, different motion sensors have performed differently depending upon e.g. study population, activities performed. While using a motion sensor in clinical settings few
considerations need to be addressed. First, type of the patient group to be examined; second, selecting the type of activity monitor i.e. type of motion sensor that suits the patient/patient group, and third, the type of outcome that is of interest. We believe that motion sensor that is validated with good reliability should be preferred.

**Paper II (Energy Intake)**

Energy intake is an important component in energy homeostasis, and its assessment is essential for nutritional intervention. The energy intake can be estimated by different dietary assessment methods. In paper II, dietary assessment methods, namely, diet history and 7-day food diary methods were validated. The results of this study indicated that both diet history and 7-day food diary underestimated the reported energy intake (28% vs 20%) in women with COPD when compared with the criterion method, DLW. Nonetheless, a higher proportion of patients were identified as valid reporters when energy intake was assessed by 7-day food diary compared with diet history (63% vs 32%). The results of this study are similar to results from other studies that reported on the accuracy of dietary assessment methods in healthy adults (112,160-164). Underestimation of reported energy intake seems to be prevalent regardless of the dietary assessment method used, or group studied (112). There may be few reasons for underestimation of reported energy intake, among which underreporting and under-eating are common (112). A generalized underreporting of food intake has been observed in different healthy groups ranging from children to the elderly (112); prevalence of underreporting in women may vary according to the dietary assessment method used (162); various physical and psychological factors may be associated with the energy intake (112, 160,161,163,165); subject characteristics such as body size, gender, smoking and socioeconomic status might also influence reporting of energy intake (112); higher BMIs and higher fat mass in women may affect underreporting; and lastly, it is also reported to be associated with social desirability, body image, and body dissatisfaction (163,165,166). In our study, the patients’ weights remained stable during the study period, implying that the underestimation of reported energy intake was more likely attributable to underreporting. Furthermore, like others (162), a higher proportion of women with COPD in our study group underreported their energy intake when assessed by diet history than by 7-day food diary and the relation of BMI and underreporting was also observed in our group of patients similar to others (163,165,166).

Many theories have been presented to explain the phenomenon of underreporting. Inaccuracy in recording energy intake may be deliberate or
subconscious (112). One possible reason for the inaccuracy could depend on the dietary assessment methods used. Retrospective dietary assessment methods rely on the memory of the participant, which may lead to incorrect data collection, whereas the prospective methods have been shown to be more accurate in assessing energy intake (111). However, these methods can be perceived as tedious and time-consuming and may thus affect the participant compliance. In our study, underestimation of reported energy intake was lower for the 7-day food diary than for the diet history method. The diet history method included averages of the foods and drinks consumed most often (≥ 2 times/month). Seasonal variation in habitual food intake, memory, and the ability to estimate portion sizes accurately may have affected the outcome of reported energy intake. On the other hand, completing a 7-day food diary may have been perceived as a burden. Because these women had COPD, a disease that places great physical and psychological stress on the patient, completing a food diary may have been cumbersome. Other possible reason for underestimation is the within-subject random variation in dietary energy intake, which may be of the magnitude of 20% to 30%, and is approximately 10% for a 7-day recording period (167).

Assessing dietary intake is a challenging task both in clinical praxis and research. To attenuate underreporting, Scagluisi et al. suggest using a motivational training program that has been developed in a manner that subjects are comfortable reporting their intake of foods considered socially undesirable in combination with confronting their earlier dietary assessment results and utilizing portion size measurement aids (168). Since women with COPD are at greater risk of losing body-weight, it is imperative to choose a dietary assessment method that provides better estimates of energy intake. Underestimation of dietary intake and its related factors must be considered, and clinicians must follow up with patients. There is a further need to develop dietary assessment methods that can ascertain true reported energy intake after adjustment for within-subject variation and the variations in the methods used.

**Paper III & IV (Energy requirement)**

The hypothesis in the paper III was that the energy requirement could be predicted within reasonable limits using pedometer-determined physical activity level multiplied by RMR equations. We found that the predicted energy requirement assessed by pedometer-determined physical activity level and five of six RMR equations had a strong agreement with the criterion method, DLW in women with COPD. The majority of the women in the study group (67%) were within accuracy limits (± 10%), and better
estimates at group level were obtained when energy requirement was predicted by WHO equation and pedometer-determined physical activity level. Similar to our results, Slinde et al. have reported that energy requirement can be assessed at group level using WHO equation (115). In their study, the WHO equation was multiplied by a factor of 1.7 to calculate energy expenditure, whereas we have used a physical activity level value derived from a pedometer.

Many reports of different populations have shown a variation in predicted energy requirements (94,95,97,115,123,169-171). We also found a considerable variation in predicted energy requirement, which could partly be due to the RMR equations used. This variability can be attributed to differences between the groups upon which these RMR equations are based and the current populations, and differences in the time line of when these studies were conducted. The variation in predicted energy requirement could also be because of using physical activity level values determined from the pedometer. The pedometer does not register activities such as cycling, bathing, or upper body movements, but these contribute to increased physical activity level and consequently to increased TEE. Secondly, pedometers have been shown to have less accuracy for registering steps taken at slower walking speed both in chronic respiratory disease patients and in healthy subjects (138,172). It is often speculated that walking at lower speeds is common in patients with COPD especially those with a severe form of the disease. COPD patients are often less active and have very low median values for steps per day (40). Considering these factors, there is a probability that the actual physical activity level was higher than the pedometer-determined physical activity level, consequently resulting in variation in predicted energy requirement. However, it can be speculated that using pedometer-determined physical activity level gives a better estimate than using a theoretical physical activity level value. There is an aggregated evidence of convergent validity stating that pedometers can be used for assessment of physical activity in both research and practice (173).

Regardless of the variation, at the group level, the predicted energy requirement in five of six RMR equations used together with pedometer-determined physical activity level was within a reasonable accuracy, i.e., ± 10% of the measured TEE by DLW method. In clinical practice, for now, it remains up to the individual health care provider as to whether and under what conditions estimated energy requirement should be used. A clinical judgment will play an important role regarding when to accept predicted energy requirement using RMR equations and pedometer-determined physical activity level in females with COPD.
In the fourth paper, all available data on TEE measured by DLW method in patients with COPD were evaluated and presented as energy requirement per kg body-weight and per kg fat-free mass. As expected, there was a substantial variation both in RMR, TEE, and activity energy expenditure. The RMR and TEE increased with increase in fat-free mass in the present study. More evidence has been emerging that fat-free mass is the primary determinant of RMR (174,175), and this seems to be related to the factors such as quantity and metabolic activity of muscles, which might be influenced by race, gender, physical activity, functional- and health status (174). The calculated RMR and TEE per kg body-weight increased, whereas, RMR and TEE per kg fat-free mass decreased with the disease severity. A few factors may have played a role; that the majority (77%) of the patients had a fat-free mass index lower than the reference values (44); muscle metabolism (174); and type and duration of physical activity. Furthermore, the patients with COPD appear to have decreased muscle capillary density, ambulatory muscle atrophy, and a shift in muscle fiber type from type I and IIa to IIb (41). The RMR increased, whereas TEE decreased with increased disease severity in the studied COPD patients, indicating a decrease in physical activity as the disease progresses. In a controlled trial, patients with COPD had a normal TEE despite an elevated RMR, and it was concluded that COPD patients reduce their physical activity level (176). The results of the present study suggest that the BMI increases with increase in lung function measured as FEV₁ % of predicted value. Reports from population based studies have suggested that not only is BMI related to disease severity in COPD, but also a low BMI is a risk factor for developing COPD (59,60).

There were differences between women and men in the present study. Despite having a higher FEV₁ % predicted, BMI, physical activity level, and energy expenditure per kg fat-free mass, women compared to the men had significantly lower RMR, TEE, fat-free mass index, and energy expenditure per kg body-weight. These differences can partly be due to a higher fat-free mass and a lower lung function in men, and probably because of the inherent gender differences. Gender correlated independently with RMR- and TEE per kg body-weight and lung function had an independent correlation with RMR per kg body-weight and TEE per kg fat-free mass.

For the purpose of applying these results in primary health care and in hospitals for calculation of energy requirement, the data are presented both by body-weight and fat-free mass. Measuring body-weight is a common practice in health care, although measuring body composition would be desirable, and is more informative to dieticians and physiotherapists particularly in the evaluation of a given intervention. Energy metabolism is a multifactorial, complex process, which is even more complicated in patients
with COPD. There is a need for larger multi-center studies in patients with COPD concerning the measurement of TEE using the DLW method to establish guidelines for calculation of energy requirement that covers affecting factors such as, age, gender and disease severity.

**Paper V (BMI OLIN study)**

The findings from the population-based study confirmed the hypothesis that the subjects with COPD are more under-weight than non-COPD subjects, and that there was a gender difference indicating that women with COPD are more likely to be under-weight than men with COPD. Further, low BMI was independently associated with COPD. Our COPD subjects had both, increased prevalence of low BMI and being underweight. A similar pattern was revealed when COPD subjects were compared to sub-groups of the non-COPD group, namely, normal lung function and restrictive spirometry pattern subjects. These findings are broadly consistent with both population-based and non-population-based studies including subjects with COPD (25,44,59,60,155,177-179). In both women and men with COPD, all GOLD stages especially those with GOLD 3-4 had a high proportion of underweight subjects when compared to women and men with normal lung function. Low BMI has been shown as an important risk factor for the development of COPD (59,60), and that being under-weight is an independent risk factor for all-cause, and COPD-related mortality in subjects with COPD, especially with GOLD 3-4 (46,52,58,62,180).

The results of the present population-based study are in concordance with the findings of other population-based studies demonstrating that the prevalence of obesity was significantly lower in COPD subjects than non-COPD subjects (29,60,177), whilst, non-population-based studies have shown a higher prevalence of obesity in COPD (178,179). Obesity in COPD seems to increase the risk for ischemic cardiovascular disease, increased dyspnea, increased inflammatory vulnerability, and more fatigue (155). It is essential to identify this group of patients for nutritional intervention that focuses on reducing body-weight and maintaining fat-free mass.

The finding that women with COPD had a significantly lower mean BMI, as well as higher prevalence of under-weight and more women with COPD were current smokers than men with COPD may have some explanatory reasons. Slimming and fear of gaining weight is common among women with COPD (53). Women seem to have a different body image compared with men and use tobacco smoking as a tool to control their body-weight (56,57). No specific pattern concerning the clinical characteristics was observed for any BMI category in women or men with COPD. Contrary to our expectation, we
did not find a significant association between BMI and FEV₁ % predicted in any BMI category except in under-weight women. The few possible contributing factors could be: The mean values of FEV₁ % predicted were similar across the BMI categories; the correlation by disease severity was not explored as there were few women and men with GOLD 3-4; and body composition was not measured and thus the lack of information regarding the distribution of adipose tissue in the body. Abdominal obesity is associated with worsening lung function, whereas peripheral obesity is associated with better lung function (181).

Different BMI cut-offs defining under-weight have been used in different studies resulting in wide variation in prevalence of under-weight (60,177-179). A recent consensus statement from The European Society for Clinical Nutrition and Metabolism (ESPEN) has recommended different BMI cut-offs for different ages to define malnutrition (182). A large collaborative study has demonstrated that BMI < 22.5 kg/m² had a strong association between mortality and smoking-related disease (58). In Sweden, in clinical praxis, the under-weight is defined as BMI < 22 kg/m² in patients with COPD (183). There seems a growing need to have a consensus on BMI cut-off values to define under-weight in patients with COPD.

**Clinical perspectives**

As mentioned previously, low BMI and low FFMI are independent risk factors for mortality in patients with COPD. Low BMI is more common in patients with COPD than non-COPD subjects. It is desirable to measure body composition in patients with COPD because it provides detailed information about the constituents of body-weight, and the effects of e.g. nutritional intervention, physical training can be evaluated more successfully. As of now, in clinical settings, BMI is a commonly used reliable measure of nutritional status, since measuring body-weight and height is practical, and feasible. The ESPEN also suggest to use BMI among other methods to diagnose malnutrition. (182). To prevent loss of body-weight, or to attain weight gain, nutritional treatment should be provided. For a successful nutritional treatment, it is imperative to assess objectively the patient’s energy expenditure and intake and calculate the energy requirement. Energy expenditure is not always equal to energy requirement. When a patient is in need of gaining or losing weight, the energy expenditure is not equal to energy requirement. The calculated energy requirement should be adjusted so that the goal of weight gain or loss is achieved.

We have validated different methods that assess energy expenditure, energy intake and energy requirement in women with COPD. Energy expenditure
was assessed reliably by the SenseWear Armband, software version 5.1, and it can be used to determine energy expenditure in women with moderate and severe COPD. These results should cautiously be extrapolated in their use in other COPD groups. Regarding estimation of energy intake, none of the validated methods fared well. However, the 7-day food diary fared better than diet history method. On the other hand, in clinical settings, using food diaries are beneficial for other reasons, such as, knowledge regarding meal pattern, choice of foods, the order of meals is attained. To evaluate the energy intake values from these diaries, it is important to obtain weight history of the patient. The energy requirement can be calculated with reasonable accuracy by common RMR equations and pedometer-determined physical activity level. These methods are beneficial in the absence of objective methods such as the DLW method and motion sensors. We have also evaluated and presented energy expenditure data from DLW studies in patients with COPD. The data are presented as energy requirement per kg body-weight and per kg fat-free mass, and may be applied in clinical settings. Further studies measuring energy expenditure in patients with COPD that include a larger population of women and men with different disease severity are warranted. The methods validated in this thesis can be used in the clinical setting. However, the health care practitioner should be aware of the limitations of these methods. We believe that for assessment of nutritional status and for providing nutritional treatment, a clinical judgment should be used regarding the application of these methods, and it is essential to follow up the results of the treatment.

**Relevance**

The population of females with COPD is increasing. Due to several factors, the risk of nutritional depletion is increased and this may have severe implications on the health of the patient. Studies concerning nutritional status, methods for evaluation of energy expenditure/intake and energy requirement in women with COPD were lacking. The present research program was directed towards a mounting clinical need. Knowledge was acquired regarding the strengths and weaknesses of different objective methods used to measure energy expenditure, energy intake and energy requirement in COPD. The findings will guide us as to how to improve the prognosis related to malnutrition in women with COPD, hence contributing to the improvement of their nutritional status and living situation. An insight into the distribution of BMI categories in a population-based material was also gained. The results may guide us in taking an optimal care of this patient group, to be able to intervene appropriately and will eventually be implied in the routine clinical care of this patient group.
Ethical considerations

The methods that were used in this thesis involved no risks for the study participants. Blood samples planned in this thesis are taken in the routine care of COPD patients by competent nurses and need no special preparation or aftercare. All other measurements were non-invasive and do not cause any discomfort for the participants. Dual energy X-ray absorptiometry (DXA) is a non-invasive medical imaging technique which exposes the participants to very low energy X-rays. Informed written consent was obtained from the participants. The identity of the patients was not revealed in the data analysis. The results were presented at the group level and no data was tracked to an individual participant.

To come to the hospital in the morning in a fasting state (paper I-IV) can be stressful for the patients and might cause some discomfort. However this is much less a problem compared to knowledge that has been gained and would benefit the patients.
Future research

Studies that accurately assess energy requirement and customize nutritional intervention with regular follow-up programs are needed. It would be valuable to validate the methods assessing energy expenditure, energy intake, and energy requirement in women and men with all the stages of COPD especially those with the severe disease, since patients with severe COPD have been shown to have the most problems with regard to nutrition, low body-weight, and low fat-free mass. Studies concerning effects of obesity on nutritional status, physical activity and health related quality of life in patients with COPD are needed, considering the growing prevalence of obesity in Sweden and globally. Furthermore, studies presenting guidelines that concern handling with the issues of underestimation of reported energy intake are needed. Dietary assessment methods that ascertain true reported energy intake must be developed. Keeping in view the limitations of dietary assessment methods, future research concerning a new approach to estimate energy intake is necessary. There is also a need to establish guidelines and recommendations for calculating energy requirements for patients with COPD that are based on larger studies in COPD concerning energy expenditure measured by DLW method. To study longitudinally, the change in BMI in relation to change in lung function would also be of interest.
Conclusions

This thesis concerning patients with COPD has shown that:

- There was a substantial variation in energy expenditure in patients with COPD.

- The total energy expenditure can be assessed with a greater accuracy by SenseWear Armband version 5.1 than SenseWear Armband version 6.1 and ActiHeart in women with COPD.

- The reported energy intake was underestimated when assessed by the diet history and 7-day food diary methods. The 7-day food diary should be, however, used with caution in women with COPD.

- The energy requirement can be predicted in clinical settings using pedometer-determined physical activity level and common resting metabolic rate equations, in the absence of objective methods.

- The compiled data from the available studies of energy expenditure in COPD measured by DLW, may be applied in clinics to calculate energy requirement in patients with COPD.

- Both women and men with COPD had a lower BMI and a higher proportion of under-weight subjects than non-COPD subjects. Further, BMI was lower, and being under-weight was more prevalent in women with COPD than men with COPD.
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