Physical Activity Pattern and Sleep Characteristics in Chronic Obstructive Pulmonary Disease (COPD)

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This is to certify that the thesis prepared

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complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) patients have decreased physical activity (PA) levels compared to healthy controls. Their diurnal PA patterns are much less documented. Disturbed sleep is another common feature in COPD. The relationship between PA and sleep has never been reported in COPD patients. The project's aims were to characterize objectively measured diurnal PA patterns and sleep quality, and explore the association between PA and sleep in COPD.

Methods: Fourteen patients (aged 71±9 years) with mostly moderate COPD (FEV_1: 58±13% predicted) participated. PA and sleep parameters (Sleep Onset Latency[SOL], Wake After Sleep Onset[WASO], Total Sleep Time[TST], Sleep Efficiency[SE%], Fragmentation Index[FI]) were assessed via actigraphy for seven consecutive days, 24 hours/day. Diurnal PA patterns were evaluated by three handling approaches: arbitrary, mealtimes and equal tertiles. The interaction of period of the day by handling approach was tested with two-way repeated-measured ANOVA. Associations between sleep parameters and mean daily PA and PA in each tertile was assessed with bivariate correlations.

Results: There was a significant interaction effect of period of the day by handling approach ($p<0.001$). Regardless of the approach**,** PA significantly decreased in the evening compared to morning and afternoon. Participants had, on average: SOL: 22±17min, WASO: 65±29min, TST: 383±59min, SE: 79±9% and FI: 45±23%. Mean daily PA and PA in each tertile showed very weak to moderate associations with sleep parameters ($r = -0.50$ to 0.42).

Conclusion: PA levels drop in the evening in patients with moderate COPD. The relationship between PA and sleep quality appears modest in these patients, but the PA-sleep relationship warrants further investigation.

Key words: COPD, physical activity, diurnal patterns, accelerometer, sleep quality

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“The capacity to learn is a gift; the ability to learn is a skill; the willingness to learn is a choice "

- Brian Herbert

Author Contributions for the Manuscript

Zohra Parwanta is the primary author of the manuscript of this thesis. She was responsible for developing the idea for this specific study, as well as for the literature review, data extraction, analysis and assembly of the manuscript.

Véronique Pepin is the main supervisor of the primary author and oversaw all stages of both the larger research project and this specific study and its related manuscripts. As the primary editor of the manuscript included in the present thesis, she also ensured the accurateness and completeness of its content.

Emilie Chan-Thim is the primary author of the parent project and generated the main idea behind it. She was responsible for recruitment and collection of data and she synchronized journal and actiwatch data for wake time and bedtime.

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List of Abbreviations and Acronyms

ABG:	Arterial Blood Gas
ANOVA	Analysis of Variance
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
DPA	Daily Physical Activity
FEV	Forced Expiratory Volume
FEV_1	Forced Expiratory Volume in One Second
FI	Fragmentation Index
FVC	Forced Vital Capacity
GOLD	Global Strategy for Obstructive Lung Disease
LTOT	Long Term Oxygen Therapy
LVRS	Lung Volume Reduction Surgery
PA	Physical Activity
$PaCO_2$	Partial Pressure of Carbon Dioxide in Arterial Blood
PaO_2	Partial Pressure of Oxygen in Arterial Blood
PR	Pulmonary Rehabilitation
PSG	Polysomnography
PH	Pulmonary Hypertension
SE	Sleep Efficiency
SOL	Sleep Onset Latency
SpO_2	Oxygen Saturation Measured by Pulse Oximetry
TIM	Time In Bed
TST	Total Sleep Time
V_A/Q	Alveolar Ventilation/Perfusion Ratio
VO_{2max}	Maximum Oxygen Consumption
WASO	Wake After Sleep Onset

Chapter I

1.0 Theoretical Context

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and manageable lung disease characterized by a progressive airflow limitation; it represents one third of the most prevalent human health disorders in the world (1). The most recent Global initiative for Obstructive Lung Disease (GOLD) guidelines define COPD as " a common preventable and manageable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lungs to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients." (2). Furthermore, COPD has both pulmonary and extra-pulmonary components that include weight lost, nutritional abnormalities and skeletal muscle dysfunction (2-4).

The term COPD has often been used as an umbrella term consisting of emphysema – which refers to the permanent enlargement of air spaces that are distal to the terminal bronchioles consequent to the destruction of alveolar walls (5) – and chronic bronchitis, which refers to the presence of cough and sputum production for at least 3 months in a year for two consecutive years. However it is important to recognize that emphysema covers only one of the structural changes present in COPD, and that chronic bronchitis is an independent disease entity and also exists in patients with normal spirometry (2). The mechanisms underlying airflow limitation in COPD can be categorized into two groups: i) changes in the airway, such as increased airway resistance, airway inflammation, small airways disease and airway fibrosis or luminal plugs, and ii) changes at the alveolar level, such as parenchymal destruction, loss of alveolar attachments and decrease of elastic recoil (2) and, as a result of these the above changes, the ability to breathe normally is reduced (5). The symptoms of COPD include shortness of breath (dyspnea), coughing, wheezing, fatigue, frequent chest infections, and an overproduction of sputum (6). COPD is also frequently associated with lung cancer and is a major contributor to the development of cardiovascular disease as well as muscular atrophy and dysfunction (7). Progression of COPD typically follows a downward spiral called the "dyspnea spiral", which initiates with airflow limitation and dyspnea, followed by inactivity and muscular

deconditioning, which in turn worsen the dyspnea sensation in patients and eventually cause invalidity and poor quality of life. Figure-1 demonstrates this “dyspnea spiral”.

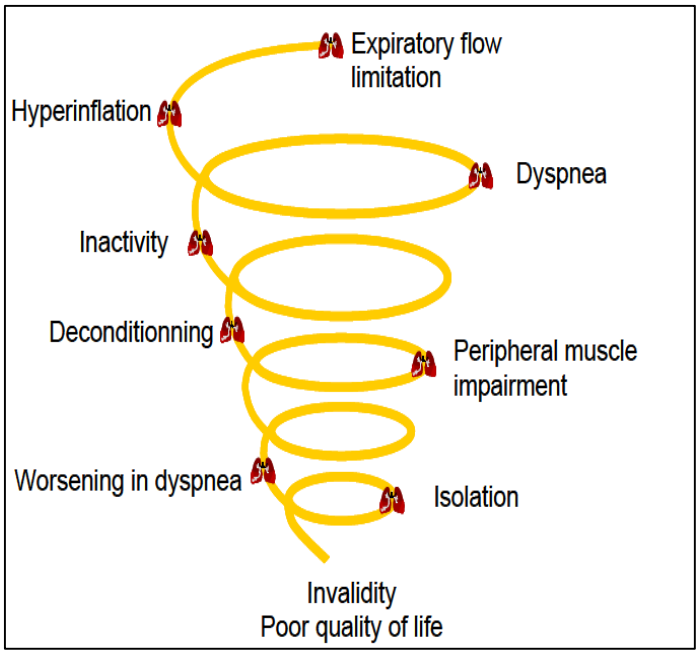

Figure 1 - COPD Downward Spiral
Adapted from la Clinique du soufflé la Solane, Osséja, France

1.1 Burden of Chronic Obstructive Pulmonary Disease

COPD is one of the leading causes of morbidity and mortality worldwide and therefore, it has substantial and increasing consequences on the social and economic status of the nation (2, 3, 8). COPD is usually not diagnosed until it is clinically apparent and moderately advanced, and therefore tends to be greatly underestimated in its prevalence and morbidity data (8). As any other chronic disease, the prevalence, incidence, morbidity and mortality of COPD varies between countries and between different age groups within a country (2).

COPD is the fifth leading cause of morbidity and the fourth leading cause of mortality (9) in developed countries and it is estimated that by 2030, it will be the third leading cause of death worldwide (10). However, due to the different definitions and terminologies used in the past, COPD has been under-recognized, under-diagnosed and under-treated (9). The increase in both mortality and morbidity of COPD is attributed to the continuous use of tobacco smoking and to demographic changes, such as the increased life expectancy in developed countries (9). In

Canada, although the disease is knowingly under-diagnosed, at least 700,000 adults (4.4% of adults 35 years and older) are reported as suffering from COPD according to a study published in 2008 (11). However, a more recent study published in 2012 showed that 1.5 million people had been diagnosed with COPD in Canada, with a mortality rate of 10, 000 deaths per year (12).

The incidence of COPD, which is the number of new cases in a certain amount of time, has also been reported in varying ranges across studies; it is therefore hard to summarize this information since it has been reported in different units and over different lengths of time. A longitudinal observational study reported a decreased in the incidence of COPD in Ontario, Canada, from 1996 to 2007 (13). The cumulative incidence rate decreased from 11.8 per 1000 adults to 8.5 per 1000 adults. The decrease was greater in men (32.3%) compared to women (24.7%) and in older adults (≥ 65years) compared to young adults.

COPD is associated with a significant economic burden, both directly and indirectly. Direct costs are those related to the detection, treatment, rehabilitation and prevention of the disease and mostly include hospital expenses, pharmacological and ambulatory care related to the COPD. Indirect costs are due to morbidity, missed work, premature mortality and disability. In Canada, the health cost for COPD was estimated at $4.52B in 2011 and is projected to reach $101.4B in societal costs over the next 25 years (12). COPD exacerbations account for the largest proportion of the COPD burden on the healthcare system and, as the disease progress, the expenses also increase with the greater cost being associated with more severe diagnoses of COPD (2).

1.2 Risk Factors

Recognition of risk factors for any disease is very important in the treatment and development of prevention measures. Generally, risk factors for a disease include host risk factors, which are endogenous, and environmental risk factors, which are exogenous (14). The current understanding of COPD risk factors are incomplete in many aspects, but it is believed that COPD results from interaction between environmental factors and different genotypes (2). The most important risk factor in developing COPD is undoubtedly tobacco smoking, as up to 50% of long-term smokers develop COPD (9). It is suggested that the risk in active smokers

varies according to the country from 40-70% (15). Studies indicate that approximately 90% of patients suffering from COPD are smokers or individuals with a past history of smoking (16). However, not all smokers develop COPD, which points toward the interaction between smoking and other risk factors such as genetics, age and sex, exposure to particles, air pollution and respiratory infections that determines one's susceptibility to COPD (9). Figure-1 provides an overview of the possible risk factors for COPD.

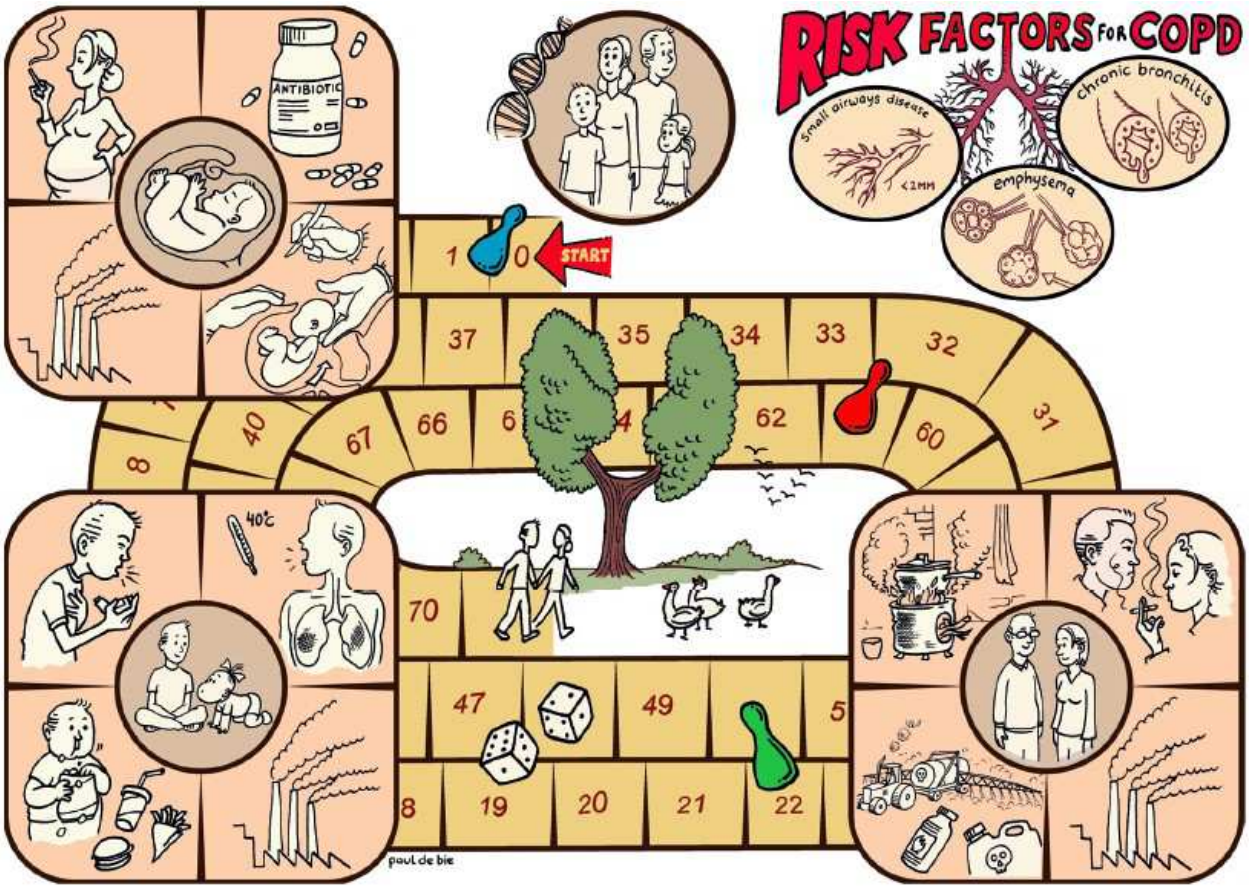

Figure 2 - Graphic Representation of the Risk Factors for COPD during Different Stages of Life.
Upper left corner: Risk factors during in utero and perinatal life, **Lower left corner:** risk factors during early childhood, **Lower right corner:** risk factors during adulthood, **Upper right corner:** General risk factors are also shown
Adopted from Dirkje. S.P. *The Lancet*, 08, 2015 (17)

1.3 Pathology, Pathogenesis and Pathophysiology of COPD

Inflammation in the lungs is a normal response to noxious particles from inhaled cigarette smoke or other biomass fuels, however this response is modified in patients who develop COPD

(2). COPD is not a disease entity, but rather a complex of conditions that contribute to airflow limitation (18). These conditions include emphysema, which is destruction of parenchyma tissue and reduced surface for gas exchange, chronic bronchitis, which is a condition of large-airway inflammation and remodelling (19) and small airway fibrosis, which is disrupt normal repair and defense mechanisms (2). Progressive airflow limitation and air trapping is the result of the above pathological changes (2). The following section will address the underlying physiological changes that cause the progressive airflow limitation.

1.3.1 Pathophysiology of COPD

The different pathogenic mechanisms that produce pathological changes in the respiratory track will cause physiological abnormalities (20), such as expiratory flow limitation and lung hyperinflation, gas exchange limitation, respiratory and peripheral muscle dysfunction, and exercise intolerance.

1.3.1.1 Expiratory Flow Limitation and Lung Hyperinflation

The term "expiratory flow limitation" indicates that maximum expiratory flow is reached during tidal breathing and indicates airflow obstruction in the intra-thoracic space (21). The American Thoracic Society has a report on "*Standards for the Diagnosis and Treatment of Patients with Chronic Obstructive Pulmonary Disease"* which documents that the major sites of airflow limitation are small airways (i.e. airways smaller than 2 mm in diameter) and the limitation is mostly due to the remodelling of those airways (8). Other contributing factors for expiratory flow limitation are destruction of alveolar support and loss of elastic recoil, which is due to destruction of alveolar walls (22). On the other hand, expiratory airflow limitation promotes hyperinflation of the lungs, which is defined as "abnormal increase to the volume of air remaining in the lungs at the end of a spontaneous expiration" (23). Expiratory flow limitation not only causes lung hyperinflation, but also increases intrinsic positive end-expiratory pressure and work of breathing, and impairs function of inspiratory muscles (24). Lung hyperinflation in COPD patients is due to increased lung compliance, which in turn decreases inspiratory capacity resulting in an increase in functional residual capacity (7). As a result of these mechanisms, patients feel breathlessness (dyspneic) on exertion or even at rest in severe stages of the disease. Hyperinflation that occurs particularly during exercise is referred to as dynamic hyperinflation.

Dynamic hyperinflation causes dyspnea and is considered one of the limiting factors for exercise capacity (8). Other contributing factors are accumulation of inflammatory cells, mucous and plasma exudate in the bronchi and smooth muscle contraction and dynamic hyperinflation during exercise (8).

1.3.1.2 Respiratory and Peripheral Muscle Dysfunction

By definition, muscle dysfunction is a loss or decrease in at least one of the main muscle functions: muscle strength and/or muscle endurance (25). Muscle endurance is defined as the ability to maintain sub-maximal effort over a prolonged period of time, where muscle strength is the ability to produce maximum contractile effort for a short period of time (26). Furthermore, muscle fatigue, which is loss of contractile function, can be chronic or acute (develop suddenly or gradually over long period of time), and partial or complete and it is resorted with rest (27). In COPD patients, all three components of muscle dysfunction, which are muscle weakness, muscle fatigue and reduced endurance are the result of complex interactions between several other factors that can be present at the same time. These factors and their biological consequences vary in respiratory and peripheral muscles, which are due to local and systematic factors (26).

Respiratory muscles in COPD patients face increased mechanical ventilator loads due to airflow limitation, pulmonary hyperinflation and increased compliance (26). The increased work of breathing and overload on respiratory muscles of COPD patients are due to the following three conditions: first, there is a decreased elastic recoil of the lung derived from changes in the thorax wall and lung parenchyma; second, there is an increased resistive load due to air passage through narrowed airways; and lastly, there is an increased threshold load derived from the intrinsic positive end-expiratory pressure (28, 29). On the other hand, static hyperinflation changes thorax geometry, causing the diaphragm to shorten (25). The condition can further get worse with dynamic hyperinflation upon exertion. This change in the optimum length of the diaphragm can affect its ability to generate force. The above changes lead to disturb mechanical demands of the respiratory system and functional capacity of the ventilatory muscles as well as the metabolic demands and energy supply to these muscles (26). Apart from the above local influences, systemic factors such as pulmonary gas exchange impairment, systematic inflammation, nutritional abnormalities, use of drugs for COPD treatment, tobacco use, and finally other comorbidities can also influence the function of respiratory muscles negatively (30-32).

About one-third of COPD patients experience peripheral muscle dysfunction, which could be due to many different factors such as systemic inflammation, systemic oxidative stress, gas exchange abnormalities, inefficiency of anabolic hormones, nutritional abnormalities, comorbidities, muscle wasting, tobacco, aging and the drugs used in treatment of COPD (26). In their review of the literature, Gea et al. (26) report that function impairment of peripheral muscles also has important clinical consequences for these patients and is associated with low exercise tolerance, reduced quality of life, greater use of health care resources, and increased mortality. It is shown that both muscle strength and endurance decrease in COPD patients. Particularly muscle strength decreases two to four times faster in COPD patients compared to healthy individuals (33, 34). It is important to note that there is a heterogeneity in limb muscle dysfunction in COPD; indeed, while some patients with mild to moderate airway obstruction exhibit muscle dysfunction, this muscle condition is absent in half of COPD patients with severe disease (35). This variability for the same level of lung function suggests that other factors, such as muscle deconditioning potentially due to a sedentary lifestyle, play a role in muscle dysfunction in COPD patients.

In summary, hyperinflation and increased preloads are the main factors for respiratory muscles dysfunction. Additionally, deconditioning due to inactivity is believed to be a main driver of muscle dysfunction in locomotor muscles of COPD patients (27).

1.3.1.3 Exercise Intolerance

One of the problematic symptom of COPD, which involves both central and peripheral factors, is exercise intolerance (36). It is shown that exercise intolerance is associated with functional impairment and disability. Additionally, it is a stronger predictor of poor quality of life and survival than either spirometry or oxygenation (37). In healthy untrained individuals, factors limiting exercise capacity are reaching maximum oxygen consumption (VO_{2max}), dyspnea, and general or leg fatigue. However, in COPD patients, exercise capacity is limited by the interaction between multiple factors such as: impairment of ventilatory and respiratory mechanics, disease symptoms, gas exchange limitations and peripheral muscle (often leg) fatigue (36). Throughout exercise, healthy subjects typically maintain their end-expiratory lung volume and inspiratory capacity stable (or changes in the advantageous direction), and increase the rate

and depth of their breathing to adapt to the increased metabolic demand of their body. On the other hand, COPD patients have a reduced rate of lung emptying due to the decreased lung recoil and increased compliance (36). During exercise, end-expiratory lung volume therefore further increases as the time for lung emptying shortens, especially when patients experience hyperinflation at rest (36), leading to dynamic hyperinflation or additional air trapping during exercise (23). This change in end-expiratory lung volume results in reduced inspiratory capacity, since total lung volume does not change (23). Further, COPD patients exhibit greater ventilation/perfusion abnormalities due to more pronounced ventilatory response for a given load compared to healthy individuals (23).

Two main exercise limiting symptoms reported by COPD patients are leg fatigue and dyspnea (38). In their descriptive study, O'Donnell et al (39) reported that both COPD patients and healthy controls used terms like "increased work/effort" and "heaviness of breathing" to describe their shortness of breath or exertional dyspnea, but terms like "unsatisfied inspiratory effort" (i.e., "can't get enough air in"), "inspiratory difficulty," and "shallow breathing" were used by COPD patients alone, indicating the presence of hyperinflation in this patient population (39). Moreover, it was shown that the intensity of exertional dyspnea is associated with the level of dynamic hyperinflation reported by COPD patients. In general, patients with moderate to severe COPD have higher perception of dyspnea than leg fatigue during exercise (40), whereas in mild stages of the disease, the opposite is more often true (36). Exercise intolerance is also affected by training status and individual susceptibility to muscle fatigue (41), exercise modalities (42), and bronchodilation status (43).

1.3.1.4 Comorbidities in COPD

COPD is a disease of old age and it comes with other comorbid conditions. The most common comorbidities that are present in COPD patients are cardiovascular diseases, lung cancer, metabolic disorders, osteoporosis, anxiety and depression, skeletal muscle dysfunction, cachexia, gastrointestinal diseases, other respiratory conditions (44), sleep disorders (insomnia and obstructive sleep apnea), and anemia (45). It has been shown that a majority of COPD patients aged 45-year and over have at least one comorbid condition (46). Similarly, another study documented that 98% of COPD patients in their cohort had one or more comorbid

condition and more than half (52%) had at least four coexisting conditions (47). Diagnosis and management of comorbidities of COPD patients are very important because evidence suggests a negative impact of comorbidities on patients' outcome such as quality of life, exacerbation and mortality (45).

1.4 Clinical Assessment of COPD

COPD is a chronic progressive lung disease that is categorized into four stages based on spirometry results by GOLD (7). Table-1 presents the four stages of GOLD.

Table 1 - Spirometry classification of COPD severity based on post-bronchodilator FEV_1

Classification of COPD severity to GOLD stages I-IV: Based on Post-bronchodilator FEV_1		
	In Patients with FEV_1 /FVC < 0.7	
GOLD Stage I	Mild	$FEV_1 \geq 80\%$ Predicted
GOLD Stage II	Moderate	$50\% \leq FEV_1 \leq 80\%$ Predicted
GOLD Stage III	Severe	$30\% \leq FEV_1 \leq 50\%$ Predicted
GOLD Stage IV	Very severe	$FEV_1 \leq 30\%$ Predicted

FEV_1: forced expiratory volume in 1 sec, FVC: forced vital capacity, GOLD: Global Initiative for Chronic Obstructive Lung Disease
Adapted from GOLD Report update, 2013 (2)

1.4.1 Diagnosis of COPD

COPD often has an initial undiagnosed phase during which the individual does not demonstrate any signs or symptoms of the disease. However, diagnosis should be considered if any of the signs or symptoms of the disease (such as chronic cough and/or production of sputum, and/or presence of dyspnea) and/or exposure to risk factors for the disease (such as smoking, air pollution, and/or history of COPD in the family) are present (20). Spirometry is the required test to confirm diagnosis of COPD (48) in combination with symptoms and medical history of the patient.

1.4.1.1 Symptoms

The four main symptoms of COPD are chronic and progressive dyspnea, cough, sputum production, and wheezing and chest tightness (7). Dyspnea is one of the major symptoms of COPD, which is described by COPD patients as "unsatisfied inspiratory effort" (i.e., "can't get enough air in"), "inspiratory difficulty," and "shallow breathing." (23). On the other hand, COPD patients can experience chronic cough, but disregard it as a consequence of smoking and/or environmental exposure (7). It is also called smoker's cough and is often the first symptom of COPD (49). However, in some cases it might be absent even in the presence of significant airflow limitation (7). It can start with occasional coughing, but may become more persistent throughout the day (7). Sputum production, which is the production of a small quantity of persistent sputum after coughing bouts, is another symptom of COPD. It is also included in the definition of chronic bronchitis, which is regular production of sputum for more than 3 months in 2 consecutive years; however, this is not the complete range of sputum production in COPD patients (2). Lastly, non-specific symptoms of COPD are wheezing and chest tightness and they vary between days and even within a day (2). Widespread wheezes can be present while listening to inspiration or expiration, where chest tightness may be present after exertion only, which could be due to isometric contraction of intercostal muscles (2).We should keep in mind that the presence of these symptoms does not confirm diagnosis of COPD and further physical examinations are necessary.

1.4.1.2 Spirometry

Spirometry, which is the most reproducible and objective measurement of airflow limitation (2), is a test that measures volume of air as a function of time as an individual inhales maximally and exhales forcefully and completely (50). It is a physiological test that is considered the gold standard for the diagnosis of COPD. Spirometry consists of a forced vital capacity (FVC) manoeuvre, which has three distinct phases. It starts with maximum inspiration followed by a blast of exhalation and continues into complete exhalation (50). Before the test starts, the technician should make sure that the breathing tube is inserted into the subject's mouth and the mouthpiece is well placed, so air does not skip (50). The test starts with full and rapid inspiration from the end of functional residual capacity, and then is followed by the FVC manoeuvre (50). The subject blows maximally through the tube into a spirometer, which

measures the time taken to empty the lungs. From this assessment, the subject's FVC and forced expiratory volume in one second (FEV_1) are measured. The ratio of FEV_1/FVC should be obtained as well, and any person having a ratio of equal to or less than 0.7 is diagnosed with potential COPD (51). The test is done post-bronchodilator and the result is compared to the normal predicted value based on age, height, race and sex (2). The test has been used in many clinical trials due to its simplicity. Therefore, it has become the bases of most treatments and recommendations (2). Even though spirometry is the gold standard of the disease, it should be used in combination with other tests, such as chest X-ray and blood tests, to determine the severity of the disease in patients (20).

1.4.1.3 Other Assessments

COPD is a progressive disease and, once diagnosed, the severity of the disease should be assessed by evaluating symptoms of the disease as well as severity of the spirometry results, existence of other comorbidities, and the risk of exacerbations (2). Assessment of COPD symptoms can be done with several validated questionnaires such as the Modified British Medical Research Council (mMRC) and the COPD Assessment Test (CAT), which are recommended in the GOLD's report 2013 report (2). However, the CAT is preferentially recommended, since it has broader coverage of the COPD impact on the patient's daily quality of life and well-being, whereas the mMRC questionnaire measures disability due to dyspnea only (2). Further, exacerbation of COPD patients, which is an acute worsening of the patients respiratory symptoms such as breathlessness, coughing and sputum production beyond normal day-to-day variation that lasts for several days and is often treated with antibiotics (52), should be evaluated in the last 12 months (2). Frequency of exacerbation is shown to increase as the disease severity increases. As such, the exacerbation rate in a one-year follow-up of patients with moderate (Gold stage 2) COPD was 0.85, compared to 1.34 for severe patients (stage 3) and 2 for very severe (stage 4) patients (53). Exercise testing, such as treadmill or cycle ergometer testing or the six-minute walk test, assess exertional dyspnea and muscular dysfunction and are also commonly used as tools to determine disease severity and treatment options (20).

1.5 Management of COPD

At any stage of the disease, COPD is manageable (11) with adequate strategy. Proper management and treatment of COPD with both pharmacotherapy and non-pharmacological interventions can lead to improved symptoms and activity levels, and better quality of life. Management of COPD should address many aspects of the disease, starting with the prevention of disease progression, controlling respiratory symptoms (including dyspnea), reducing the frequency and severity of exacerbations (and associated treatments), improving exercise tolerance and quality of life and reducing mortality (11). Further, the management of COPD can be divided into prevention methods aimed at reducing risk factors – such as smoking cessation, decreasing occupational exposure to dust and air pollution, and increasing awareness of the disease – and intervention methods like pharmacotherapy, pulmonary rehabilitation, self-management, oxygen therapy and surgery. Since the disease is progressive and impacts different aspects and levels of one's life, a stepwise management that is comprehensive is recommended. Figure 1-illustrates the recommended treatments/interventions for COPD according to disease severity (54).

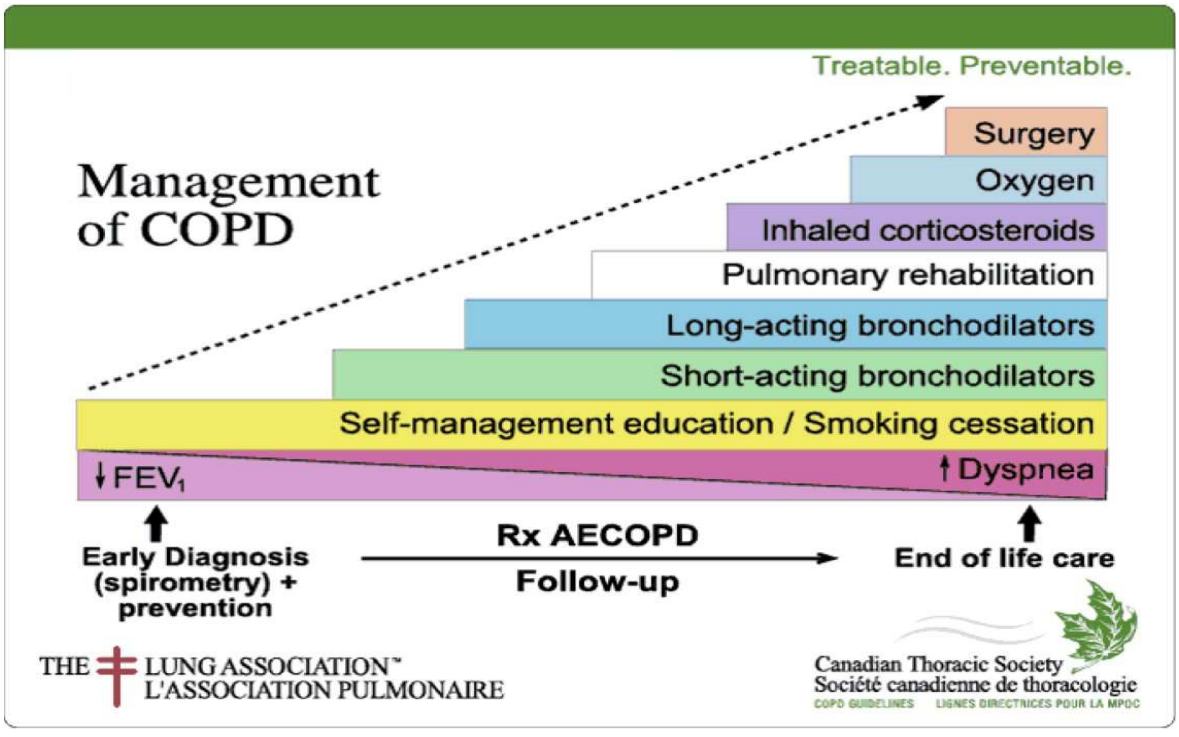

Figure 3 - A Comprehensive approach to the management of chronic obstructive pulmonary disease (COPD)

1.6 Physical Activity in COPD

Daily physical activity (DPA) has been shown to be a predictor of survival in the general population (55). Furthermore, it has been shown that in both men and women, physical inactivity increases with age, especially in individuals between 65-74 years of age and over 75. After the age of 74 in both sexes, regular physical activity (PA) is shown to decline considerably (56). Consequently, physical inactivity is already a concern in healthy older adults; in COPD patients, the scenario worsens (57). COPD is considered a disease of old age, mostly due to its manifestation after the age of 40. Additionally, an extensive literature review by Vorrink et al. (57) suggests that levels of DPA, including duration, intensity and counts of DPA, decrease significantly in COPD patients compared to healthy adults of similar age, sex and BMI. However, the extent to which physical inactivity affects the progression of COPD is not clear (57). Katajisto et al (58) have shown that patient's perception of dyspnea is positively associated with their level of physical inactivity and is disproportionally greater in relation to the decrease in lung function in inactive compared to active patients. In the last decades, measurements of daily PA have become an important outcome in COPD patients.

1.6.1 Benefits of PA in COPD

The advantage of exercise and PA on the physical and psychological well being of an individual is well documented (10). In COPD patients, PA is shown to be a predictor of all cause mortality (59). PA has been shown to have an inverse relation with hospital admission due to exacerbation (60) and all cause mortality rate in COPD patients (59, 61). This is further confirmed in a recent study showing that low intensity PA negatively affects the risk of COPD hospitalization, however this was not shown with high-intensity PA (62). Yet, it was previously suggested that any level of moderate to vigorous PA significantly decreases 30-day hospital readmission in COPD patients (63). Garcia-Aymerich et al. (61) documented that COPD patients with higher PA levels seem to have better functional status, such as better diffusing capacity for carbon monoxide (D_{LCO}), maximum oxygen uptake (VO_2), maximal expiratory pressure (P_{EMAX}) or in other terms, higher expiratory muscle strength, less systematic inflammation, and a better performance on the six-minute walk test (6MWT), which in itself is a predictor of all cause mortality in COPD patients (59). It is suggested that determining PA levels (using for example

the Baecke questionnaire) can help in predicting frailty in both stable and exacerbated COPD (64). PA is also shown to reduce use of short-acting bronchodilators (60). Last but not least, it is important to recognize that PA is also shown to have significantly positive association with health-related quality of life (HRQL) in this patient population (65).

Additionally, PA is also shown to have a protective effect on the risk of developing COPD by reducing the decline in lung function that is related to smoking (66). PA reduces oxidative stress and the prevalence of upper respiratory infections, which could be due to its anti-inflammatory response. This may explain the decrease in the detrimental consequences of smoking (67). Several longitudinal studies on lung function have also documented an inverse relationship between decline in FEV_1 and PA; they have shown a lower decline in lung function (FEV_1) with increased PA (68, 69) and greater declines in lung function (FEV_1) with lower PA levels (70, 71).

1.6.2 Recommendations of PA for COPD

Generally, PA recommendations address healthy populations, and PA recommendations for specific diseased population are either not clear (72) or not available. Available recommendations for healthy adults by the American College of Sports Medicine (ACSM), the American Heart Association (AHA) (73) and the Canadian Society of Exercise Physiology (CSEP) (74) suggest 30 minutes of moderate PA for at least 5 days of the week, or 20 minutes of vigorous PA for at least 3 days of the week for older adults. Conversely, there are no specific guidelines for COPD patients, but there are a few suggestions for diseased populations in general. The World Health Organization (WHO) (75) recommends that adults with health problems who are not able to follow the above recommendations for PA should stay as active as their conditions allow them to. Further, ACSM (73) encourages elderly populations with chronic illness to adjust their PA level to their aerobic fitness and not use the absolute measures of intensity, since these measures do not take into account individual characteristics of patients such as disease severity and fitness levels. The recent recommendations published by ACSM (76) for prescribing individualized training programs based on objective measures such as oxygen uptake or heart rate for healthy individuals of all age groups can be prescribed to individuals with chronic illnesses, provided that it is individualized with proper evaluations and guidance. The

advantage of personalized recommendations is that, unlike absolute recommendations, they take into account individual's aerobic fitness level and select the intensity of PA required to meet recommendations on the patient's individual aerobic fitness level.

As mentioned previously, there are no specific guidelines for DPA in COPD. To date, one study by Hartman et al. (72) has examined 7 different types of recommendations (three absolute and four relative and individualized) in COPD patients. They documented that agreement between different PA recommendations were poor and the percentage of COPD patients meeting the recommendations ranged between 22 to 86%. Patients with light to moderate COPD (GOLD stage I and II) met the absolute recommendations better than the individualized recommendations, while patients with severe and very severe COPD (GOLD stage III and IV) met more the individualized recommendations based on their aerobic fitness levels. The former group (GOLD stage I and II) had significantly higher mean value for moderate intensity in the individualized recommendations compared to the absolute recommendations ($p < 0.001$), and in the later group (GOLD stage III and IV), the mean value for moderate intensity was lower in the individualized estimates compared to absolute measures of intensity ($p < 0.001$). However, when pooling all patient (GOLD stage I to IV) in one group, no significant difference was found between individualized and non-individualized recommendations.

1.6.3 Measurements of Physical Activity in COPD

To begin, it is important to differentiate between daily PA and exercise. Exercise is a planed, structured, and repetitive movement with the purpose of maintaining or improving one or more components of physical fitness [23]. On the other hand, PA is any body movement, which is produced by skeletal muscles and causes energy expenditure beyond the basal metabolic rate, or resting energy expenditure (77). DPA includes, but is not limited to, exercise. Additionally, it is suggested that DPA might not have substantial effects on health outcomes of active individuals, but in less active and sedentary individuals such as COPD, it might greatly impact their well-being (78).

DPA can be assessed by direct observation, direct methods of free energy expenditure (EE) assessments (e.g. doubly labeled water (DLW), direct or indirect calorimetry), subjective

measurements (questionnaires or self-report) and objective measurements (motion sensors) [25]. The first two (direct observation and direct EE assessment) are rarely used due to impracticality, cost and availability, and because they demand highly skilled technicians (79). Therefore, other assessment methods such as subjective assessments (self-report, questionnaires, subject recall, and journals) and objective assessments (accelerometer and pedometers) are commonly used in most populations including COPD population (80).

1.6.3.1 Subjective Measurements of DPA

Subjective assessment of DPA includes questionnaires, self-reports, interviews and journals, and strongly relies on a person's ability to recall details of DPA as well as on their personal judgment (over or under estimating their PA). To some degree, it can assess different aspects of PA, including duration, intensity and type of PA. There are both advantages and disadvantages associated with subjective assessment of DPA.

Subjectively quantifying DPA has the paramount advantage of being simple and inexpensive. These methods are easy and can be self-applied, therefore, they often do not require skilled technicians, which further make them inexpensive to use. They can be applied from long distance, either by phone or mail, and even email. Therefore, participants do not have to come to a certain location in order to complete the questionnaire. An important point to keep in mind is that self-administered questionnaires should be short and easy to understand. Simple questionnaires have been shown to have high coefficients of validity and reliability (81). They are also more convenient for participants since they do not have to wear a motion sensor.

However, the downside of subjective assessment is recall bias, which refers to the possibility that participants may not properly remember characteristics of the activity, such as intensity or duration, and mostly depends on the individual patient's ability to recall and/or judge his/her level of PA. As a general rule of thumb, shorter periods of recall are suggested to minimize recall bias, which may help participants to better judge their PA levels. Further, PA questionnaires do not differentiate individual characteristics of participants, such as body weight, which might influence the reliability of the estimated energy expenditure from activities (82). In addition, while using questionnaires, the length and complexity of the instrument should seriously be evaluated. While long questionnaires may bore subjects and decrease rate of return

(especially if it is mailed), short questionnaires may limit the quantity of information received. Further, complex questionnaires may confuse the participant and decrease both the rate of return and the quality of response. The reliability and validity of questionnaires used should be tested against the gold standard, and if necessary should be modified for specific populations like COPD.

There are many PA questionnaires, however, there is no recommendation on which questionnaire is most suitable to measure physical activity for elderly, and let alone one specific to COPD patients. For the elderly population, The Physical Activity Scale in the Elderly questionnaire has documented validity (83). Similarly, some physical activity questionnaires have been modified for COPD patients (79), such as the Lengthy Minnesota Leisure-Time Physical Activity Questionnaires, and Modified Baecke Physical Activity Questionnaire, with the later one having modest validity in COPD (79).

1.6.3.2 Objective Measurements of DPA

Pedometers and accelerometers are used to quantify PA during certain amounts of time (79). As their relative names suggest, pedometers, which are worn on the hip, provide step counts, while accelerometers, which are worn either on hip, arm, wrist, or ankle, sense body acceleration. Accelerometers can be uniaxial, biaxial or multi-axial, providing movement data on one direction, two directions or multiple directions, respectively.

Pedometers are generally small instruments that are simple and relatively inexpensive (79). It has been shown that pedometers provide enough information to differentiate between different levels of PA in healthy adults (84). However, this is not documented in COPD patients (79). Furthermore, it has been shown that pedometers may underestimate the amount of PA, especially in sedentary populations with a slow walking pace (85). This could very well be the problem in COPD patients due to their slow walking pace, suggesting that pedometers may not be the appropriate device for the measurement of PA in frail populations (79). The pedometers suggested (especially during walking exercise) in COPD patients is Omron, since its reliability and precision is documented in continuous walking in COPD patients (86).

On the other hand, accelerometers are technologically more advanced than pedometers and can monitor and record data on quantity and intensity of movement (79). As mentioned previously, they can be uniaxial (monitoring data in one direction only) or multi-axial (monitoring data from multiple directions). The output of uniaxial accelerometers can be compared with pedometers since they are both in one direction, but accelerometers provide further information on the intensity of PA and PA in different periods of time (79). Multi-axial accelerometers are more advanced than uniaxial accelerometers in monitoring and storing data. Some devices also provide data on body position (lying down, sitting and standing) and different types of PA. However since they are more advanced, the cost to use these devices in clinical settings is also high and they also add to the need for technical expertise and specialized software (79).

The major disadvantage associated with many types of accelerometers available is that their output varies between models (activity count, energy expenditure, PA level, vector magnitude unit, etc.) of different companies and therefore this makes it almost impossible to compare the final results between them. This variability in the output is due to the use of different algorithms by different models. Also, accelerometers can give false or in accurate readings in activities with static trunk, (79), or static wrist when the accelerometer is on the wrist, or by recording noise such as car vibrations as body movements.

To date, multiple accelerometers and pedometers have been used to monitor DPA in COPD patients. Bossenbroek et al (87), in their systematic review of *Daily Physical Activity in Patients with Chronic Obstructive Disease,* documented 17 studies using objective methods to monitor DPA. The most frequent accelerometer used was the DynaPort accelerometer (used in 8 studies). Furthermore, validating six activity monitors against indirect calorimetry (VO_2) showed that triaxial accelerometers provided more valid results compared to uniaxial accelerometers. Both minute-by-minute, and 59-minute average correlations between VO_2 and output of activity monitors (Dynaport MiniMod, Actigraph, GT3X, SenseWear Armband and RT3) were high. For average 59-minute output, three triaxial monitors (SenseWear ($r = 0.76$), Actigraph ($r = 0.49$) and MiniMod ($r = 0.45$)) and one uniaxial monitor (KenZ Lifecorder ($r=0.52$) had the best correlations. However; the MiniMod and Actigraph were better in detecting different walking

speed (r = 0.94, r = 0.88, respectively) (88). It was shown that activity monitors were capable of detecting activity levels within the range of 1 to 1.5 METs in COPD patients.

There have thus been great technical improvements in devices to measure DPA. Yet, subjective methods remain the primary approach in measuring PA in epidemiological studies. Their reports can be further validated through the use of objective measurements such as pedometers and accelerometers. However, in clinical research, where accuracy is important, objective methods such as pedometers, accelerometers, and accelerometers with physiological sensors may be better options (79). Besides, using both subjective and objective methods concurrently can be beneficial in obtaining more reliable results. Recently, studies have used the combination of short patient-reported questionnaires and two activity monitor variables to provide valid and reliable measures of PA in COPD patients (89).

1.6.3.3 Levels of PA in COPD

Due to its important implication in health outcome of COPD patients, there is a vast body of research on levels of DPA in COPD patients. The majority of the studies have focused on levels (90-94), duration (95-103) and intensity (95, 96, 98, 99, 102, 104, 105) of PA as well as overall activity counts (92, 93, 97, 100, 102, 106). In general, they have documented a significant decrease in DPA in COPD patients compared to their healthy counterparts. Also, it is well documented that COPD patients spend more time sitting and lying down versus standing and walking in comparison to healthy elderly subjects (96, 107). Moreover, Pitta et al. (107) showed that COPD patients had significantly slower walking movement (lower intensity during walking) compared to healthy controls.

Additionally, this decrease in PA level is shown to progress across different stages of the disease and DPA is shown to have an inverse relationship with the disease severity (61, 92, 97, 108). A recent 3-year longitudinal study on disease progression and changes in PA in COPD patients showed that, over time, PA decreases significantly from baseline across all stages of COPD (109). Moreover, Watz et al. (92) documented that the level of PA, number of steps per day, and minutes of at least moderate activity decreased across clinical stages of GOLD. The above variables also decreased from patients with chronic bronchitis to patients with stage IV COPD. They further showed that, compared to patients with chronic bronchitis, the percentage of

inactive COPD patients increased in GOLD stage I, and BODE score 0, and the percentage of very inactive COPD patients increased in GOLD stage III and IV and BODE score 2 or more. Additionally, Troosters et al. (97) documented that number of steps per day as well as time spent at moderate PA levels decreases across all stages of COPD compared to healthy controls, with a significant decrease ($p < 0.005$) being reached as of GOLD stage II. It is also shown that number of steps per day, time spent walking, fast walking and total time walking decrease significantly across the GOLD stages II-IV, and a significant negative association between total walking time and GOLD stage (R=-0.35, $P < 0.0001$) is reported (108). Likewise, duration of PA and frequency of PA bouts were documented to decrease across GOLD stages (110). However, looking at time spent in vigorous PA, no significant difference was found between GOLD stages II-III and IV (102).

Additionally, studies have examined the relationship between spirometry outcomes and daily PA to determine the significance of disease progression on levels of DPA. A majority of studies have examined the relationship between FEV_1 % predicted and markers of PA, and a positive association between FEV_1 % predicted and the following PA variables was documented: standing time per day (96), number of movement per day ($r = 0.62$, $p<0.001$) (111), leg activity ($r = 0.57$, $p<0.001$), time spent mobile ($r = 0.51$, $p<0.01$) (91), overall activity count ($r = 0.41$) (100) and daily levels of PA (109). Also, Hernandes et al. (96) documented a positive correlations between time spent standing and FEV_1/FVC and maximum voluntary ventilation ($0.41< R <0.43$; $P < 0.05$). Finally significant decrease in domestic PA is shown in patients with LTOT compared to patients without LTOT ($p<0.001$) (106).

Furthermore, the association between PA and clinical characteristics and/or symptoms of COPD also has been investigated in multiple studies. Symptoms that are commonly examined are fatigue, dyspnea by MRC (Medical Research Council) scale, exercise tolerance capacity measured by the 6MWT. Measurements of clinical characteristics include BODE (a multidimensional composite measure of BMI, airway abstraction, dyspnea and exercise capacity) and quality of life mostly using Saint George's Respiratory Questionnaire (SGRQ). Watz et al. (92) documented an inverse relationship between steps per day, PA levels and minutes of at least moderate activity and both BODE and MRC scores. They further documented that compared to patients with chronic bronchitis, percentage of inactive COPD patients increased in patients with

BODE score 0 (patients who have the sensation of dyspnea on exertion) and the percentage of very inactive COPD patients increased in patients with BODE score 2 or more. Similar results were found by Jehn et al. (104), where total walking time and fast walking were significantly associated with BODE index > 6 (p=0.029 and p=0.040, respectively). In a recent study by Van Remoortel et al. (95), it was documented that patients with mild symptoms of dyspnea as well as low 6MWT and low maximal oxygen uptake had significantly lower physical activity levels. However, the study by Tabak et al. (105) found no significant relationship between physical activity levels with fatigue and dyspnea in this patient population.

1.6.3.4 Diurnal Pattern of PA in COPD

Extensive amount of research is conducted to evaluate PA levels in the general population as well as in COPD patients; however, not many studies have evaluated diurnal PA patterns not only in COPD patients, but also in the general population, young and old (112). Diurnal patterns have been observed in parameters of lung function (FEV1 and FVC), respiratory muscle strength (113), symptom perception (114), response to exercise testing (115) and to some extent in DPA(105). Moreover, while it is shown that symptom perception is worse in the morning, daily PA and parameters of pulmonary function have been shown to decrease in the evening (8:00-5:00). Yet, the significance of various diurnal patterns of PA is not known. However, equally distributing daily PA is believed to improve patients' management. Indeed, COPD patients are advised by healthcare professionals to balance their energy expenditure throughout the day by alternating heavy and light activities (105). Yet, there is no PA literature to support this recommendation.

Better understanding diurnal PA patterns in COPD patients could thus help optimize interventions targeting PA levels in this patient population. In the literature, studies examining diurnal PA patterns are scarce, both in the general population and in COPD patients. One study conducted in an elderly healthy population (mean age = 73 ± 3 years) showed that participants were mostly active from 6 to17h and that activity levels then decreased in the evening (116). In COPD patients, to our knowledge, only one study by Tabak et al. (105) evaluated diurnal patterns of PA. They too reported a significant decrease in activity levels from the morning (8-13h) and afternoon (13-13h) to the evening (17-20h) in unemployed COPD patients (n = 32). They also observed the same pattern, but not statistically significant, in employed COPD patients

(n = 7) and unemployed healthy controls (n = 10). Conversely, in employed healthy controls (n = 11), they reported an "A-shape" pattern, where PA levels peaked in the afternoon, but were similar between morning and evening (105). Of note, the healthy control group in Tabak et al.'s study (105) was significantly younger than the COPD group. Overall, it is therefore difficult at this point in time to delineate the role of COPD per se versus factors associated with the disease (age, employment, etc.) on diurnal PA patterns

Nevertheless, two methodological limitations related to PA monitoring may have affected their findings. First, the monitoring window in their study was relatively short (three-four days), and there was no mention of the respective contribution of weekend and weekdays. PA monitoring guidelines suggest a minimum of three-four days of monitoring with one weekend day to reach at least 80% of reliability; however, seven days of monitoring is preferred, as it represents the full week and allows for at least 90% of reliability (117). Another limitation of their study was the data handling approach used to determine onset, offset and splitting of the days. Indeed, an arbitrary handling approach was used, where day onset was fixed at 8:00, day offset was fixed at 20:00, and morning/afternoon/evening went from 8:00 – 13:00, 13:00 – 17:00, and 17:00 – 20:00, respectively. This was the case for all participants, regardless of their individual daily routines. Hours outside the 8:00 – 20:00 window during which participants were awake were therefore excluded, and the different portions of the day were unequal in time and not representative of any particular event (e.g., meals). Additional research is warranted to further examine diurnal PA patterns in COPD patients using more empirical and ecological data handling approaches. Also, examining the link between PA patterns and other lifestyle factors may provide valuable insight for an optimal self-management

1.7 Sleep in COPD

"Sleep is that golden chain that ties health and our bodies together" (Thomas Dekker, 1572-1632). Sleep is needed as an essential part of human life to maintain physical and psychological health (118), as well as the body's circadian rhythm (119). Sleep disturbances are associated with increased cardiovascular risk factors, stroke, type 2 diabetes, fatigue, lethargy, impaired cognition, and over all poor quality of life (120-122). Furthermore, the importance of sleep quality increases in cases of chronic, systematic and progressive disease like COPD (123).

Sleep has numerous effects on breathing such as changes in central respiratory control, lung mechanics and muscular contractility. The above changes are harmless and do not effect healthy individuals, but could impact COPD patients by resulting in significant hypoxemia and hypercapnia, particularly during rapid eye movement (REM) (124). Healthy subjects may also experience some mild hypoxemia, which is the result of trivial hypoventilation. However, this may become worse in COPD patients due to other factors impacting hypoventilation, such as air way obstruction, muscle dysfunction and diminished respiratory drive in addition to ventilation-perfusion mismatching (V'/Q')(118) and some COPD medications (125).

1.7.1 Measurements of Sleep in COPD

Similar to PA, sleep can also be assessed both subjectively and objectively. Subjective methods include questionnaires and self-report methods. As mentioned in the PA measurement section, subjective assessment methods are based on individual patient's recollection and judgment; therefore, it could be impacted by recall bias. On the other hand, objective measures provide more precise and detailed information, not only about sleep duration, but also sleep architecture, such as different sleep stages (non rapid eye movement: NREM or rapid eye movement: REM, slow wave sleep: SWS), amount of time awake during sleep periods, and frequency and duration of wake times after sleep onset (126). Objective assessment tools include polysomnagraphy (PSG), which is the gold standard for sleep measurement, and activity monitors/accelerometers, frequently referred to as actigraphy (127). Even though PSG is the gold standard and provides extensive details about sleep behaviour of an individual, it is also very expensive and can be too invasive to be used in clinical studies, especially when the primary focus of the study is sleep and/or wake duration (128). On the other hand, actigraphy is simple, inexpensive and less time consuming compare to PSG and it is independent of patients' ratings and personal judgments of their sleep. Additionally, actigraphy has been validated for sleep against PSG in young and older subjects, in healthy and in chronic primary insomniac patients, with overall high sensitivity (0.965) and accuracy (0.863), but low specificity (0.329) (129). Actigraphy provides estimates of sleep/wake schedules based on differences in movements associated with wakefulness or sleep (128), and position of the body (lying down). Further, actigraphy can conveniently allow for 24-hour continuous data monitoring for multiple days, weeks or even longer, something that is not achievable with traditional PSG (130). Previous

studies have used reliable subjective (131) and objective (131, 132) methods to assess sleep quality in COPD patients.

1.7.2 Sleep Related Disturbances in COPD

Disturbed sleep is common in COPD patients (124, 133) and it is one of the most common symptoms reported in this patient population (125). It is suggested that around 40% of COPD patients report disturbed sleep (134) and a majority of COPD patients have sleep efficiency in the range of 50-70% (125). Moreover, COPD patients have difficulty falling and/or staying asleep, more light sleep and less deep sleep (REM), increased micro arousals and recurrent shift between sleep stages (125). COPD patients report diverse sleep disorders such as insomnia and obstructive sleep apnea, and sleep related disturbances such as sleep related hypoxemia, sleep hypoventilation, and restless leg syndrome (135).

Insomnia is characterized by difficulties falling and/or staying asleep, waking up too early or having un-refreshed sleep (135). Budhiraja et al. (131) documented that the prevalence of insomnia is three-fold higher in COPD patients compared to the general population. They further reported a higher prevalence (27.3 %) of insomnia, which was defined as chronic sleep disturbances related with impaired daytime functioning in COPD patients. In the same cohort, they reported actigraphy-measured shorter sleep duration and lower sleep efficiency in COPD patients with insomnia compared to those without it. In another study they showed that the presence of COPD was significantly associated with increased odds of insomnia 1.9 (1.5–2.5, $p < 0.001$) (136). They further reported low sleep efficiency (<82%) in a larger proportion (44%) of COPD patients compared to individuals without COPD (31%). Another study documented that frequency of insomnia was higher in COPD patients compared to healthy controls (47.2 % and 25.7 %; respectively). However, they also reported that 21.3 % of the variance between the groups was due to more physical illnesses and depressive symptoms in COPD patients (137). Similar results were shown in a more recent study, where prevalence of insomnia was 48.1% in COPD patients compared to 27.6 % in healthy controls (138).

Also, the association between COPD severity and prevalence of insomnia is not clear (135). One longitudinal study looked at the association of disturbed sleep and COPD outcomes

and they documented a significant association between sleep disturbances (difficulty falling asleep, night time awakenings, morning fatigue, and sufficiency of sleep duration) and patients' symptoms such as cough ($p = 0.034$), and dyspnea ($p = 0.004$) (123). They also reported increased likelihood of sleep disturbances with greater disease severity ($p = 0.015$), whilst another study did not find a significant association between FEV_1 and insomnia symptoms (131).

Obstructive sleep apnea (OSA) is a chronic sleep disorder, which is characterized by repeated episodes of upper airway collapse during sleep, influencing night time sleep quality and daytime fatigue and sleepiness (139). Prevalence of OSA in COPD is considered to be similar to that of the general population (about 10 to 30%) (140-142). Moreover, both OSA and COPD are common pulmonary disorders and prevalence of their coexistence is about 1% in the general population (143), which is called overlap syndrome. However, it is also shown that sleep disordered breathing is more severe when it coexists with COPD (140). Among other factors, decreased exercise capacity can lead to obesity and muscular deconditioning, which in turn may lead to increased upper airway collapsibility. These are considered to be plausible factors in increasing occurrence of overlap syndrome (135)

Sleep related abnormalities and primary sleep disorders that are frequently associated with COPD thus include insomnia, OSA, restless leg syndrome, sleep related hypoxemia, and sleep hypoventilation. Co-occurrence of the above factors with COPD may further deteriorate the quality of life of COPD patients by increasing risks of other health conditions (i.e. depression, anxiety, panic attack, severe and/or chronic pulmonary hypertension) including increased mortality rate of up to 7-fold (135).

1.8 Association between PA and Sleep in Older Adults

Both PA and sleep are important health related lifestyle factors that decrease with age, and remain modifiable well into the later life (144). More recently, evidence has suggested a possible reciprocal relationship between these two lifestyle factors (145-148). Epidemiological studies consistently suggest that both acute and chronic exercise improve sleep, such that greater levels of PA are associated with better outcomes in sleep measurements (149). Similarly, some clinical studies have documented the effect of exercise on sleep quality (150-152). In two different

studies, King et al. (150, 151) reported a positive association between exercise and both objectively (PSG) and subjectively (self-reported) measured sleep quality in individuals with poor sleep. Likewise, two meta-analyses reported modest improvement in several sleep parameters including total sleep time (TST), slow wave sleep and REM sleep latency after an acute bout of exercise (149, 153). Similarly, another study in women with insomnia reported that TST, sleep efficiency (SE) and self-reported global sleep quality improved after 16 weeks of exercise, and exercise session duration was negatively associated with ratings of sleepiness at baseline (147). It is suggested that no improvement (154) or modest improvement observed in sleep could be due to healthy subjects with good sleep quality (154).

However, studies examining the association between DPA and sleep parameters are scarce and have contradictory findings. Whereas, a longitudinal and cross sectional study with 14,001 older adults documented an inverse association between habitual PA and both prevalence and incidence of insomnia, particularly improved the ability to stay asleep (146). Similarly, better initial sleep quality was shown to project greater levels of PA, beyond the effects of initial PA levels in a 2-year longitudinal study in healthy older adults. However, the initial PA levels did not predict later sleep quality after adjusting for prior sleep quality (145). Conversely, other studies have documented no association between PA and sleep in older women (148) and normal sleepers (154).

The temporal relationship between PA and sleep parameters has also been examined and certain associations between them are documented. One study with subjective reports of sleep in women with insomnia reported that poor sleep quality on a given night was associated with shorter exercise duration the following day, but exercise duration during the day did not predict next night sleep quality (147). Another study in older women with objective measurements of both sleep and PA reported two small findings: 1) they documented that greater daily PA and more minutes of moderate to vigorous PA were temporally associated with less TST the following night. 2) Higher SE and less sleep fragmentation were associated with greater PA counts and more minutes of moderate to vigorous PA the following day (148).

Moreover, the reciprocal relationship between PA and sleep is documented in the general and diseased populations. One study in patients with chronic pain reported that sleep quality is a

significant predictor of next day PA, such that nights with good sleep quality was followed by days with greater PA, especially between noon to 11PM (155). In addition, a review article on the *The Role of Sleep and Physical Activity on the Risk for Cardiovascular Disease* highlighted the importance of considering poor sleep quality as a barrier to the maintenance of regular PA (156) (Appendix A). Similarly, in COPD patient, one study documented a significant inverse correlation between functional exercise capacity (as measured by the six-minute walk test) and subjective sleep quality (157). Yet, to our knowledge, the relationship between daily PA and sleep has never been investigated in this patient population.

In summary, increased regular PA is shown to be associated with improved sleep parameters and over all better sleep quality. Therefore, increased and regular PA may have more importance for individuals with poor sleep quality than normal sleepers. Further, sleep quality can also impact PA levels in both long and short-term periods, which could be an important factor in individuals with reduced PA levels.

1.8.1 Possible Mechanisms for the Association between PA and Sleep

There are some suggested mechanisms through which these two lifestyle factors may influence each other. The recent review by Chennaoui et al. (158) summarizes the suggested mechanisms in two diagrams. According to their review, acute moderate-intensity aerobic exercise affects core body temperature, the endocrine system and metabolism (increase growth hormone, and decrease insulin sensitivity), and inhibits some parts of autonomic nervous system (ANS). On the other hand, regular moderate-intensity aerobic PA affects all of the above in addition to the immune inflammation response during sleep, mood and possibly circadian rhythm. From the above changes, core body temperature is shown to be inversely associated while circadian rhythm and mood are shown to be directly associated with improved sleep time and slow wave sleep. Further, changes in the endocrine system and metabolism, ANS and immune-inflammation response during sleep may also be related with improved sleep time and slow wave sleep.

Sleep loss is considered to have substantial psychological affects; however the effect of chronic sleep loss on physical exercise in healthy individuals is not fully understood (158). In

their review, Chennaoui et al. (158) summarized that acute sleep loss may disturb metabolism (increase insulin resistance) and immuno-inflammation response, and chronic sleep loss may affect central nervous system (CNS), endocrine system (increase cortisol, decrease growth hormone) and ANS (increase sympathetic activity). Through more complex pathways, the above changes may further affect alertness, mood, articular and muscle repair, coronary arterial tonus and heat tolerance, which may further cause reduced physical performance, reduced recovery and increased exercise induced diseases.

Chapter II

2.0 Rationale

The literature widely suggests that physical activity and exercise training have many benefits for the physical and psychological well-being of an individual (159). However, COPD patients are often too limited by their symptoms to stay active (160). Even regular daily activities can become unsustainable due to increasing levels of dyspnea, eventually leading to further inactivity (161). This subsequently leads to muscular deconditioning, creating a vicious cycle that can quickly and severely deteriorate the quality of life of COPD patients (161). It has been shown that increased physical activity is directly associated with a reduced rate of hospital admission and increased survival rate in this patient population (66). Therefore, the evaluation of PA levels in COPD patients has become an important area of research in the past decades.

As documented in an earlier section (*Levels of PA in COPD*), levels of PA have been consistently shown to be significantly lower in COPD patients compared to healthy controls. However, there is a scarcity of literature on diurnal PA patterns in the general population as well as in COPD patients. Yet, equally distributed daily PA is believed to improve patients' management. Indeed, COPD patients are advised by healthcare professionals to balance their energy expenditure throughout the day by alternating heavy and light activities (105). There is currently no PA literature to support this recommendation. Better understanding diurnal PA patterns in COPD patients could help optimize interventions targeting PA levels.

As discussed previously (*Sleep in COPD*), disturbed sleep is another common feature in COPD patients (124, 133) and it is the third most frequently reported symptoms after dyspnea and fatigue (125). Recent evidence has suggested a possible reciprocal relationship between physical activity and sleep in the general and elderly populations (145-148). However, to our knowledge, the potential association between daily PA and sleep has never been investigated in COPD patients. Exploring links between these two modifiable lifestyle factors may provide valuable insight for an optimal self-management.

Chapter III

3.0 Research Objectives and Hypotheses

3.1 Research Objective

I. To characterize, in COPD patients, diurnal patterns of objectively assessed PA from morning to afternoon to evening using three different splitting approaches (arbitrary, mealtime, equal tertiles).

II. To characterize objectively measured sleep quality in COPD.

III. To explore the association between daily PA and sleep quality parameters in COPD.

3.2 Research Hypotheses

I. Based on earlier findings from Tabak et al. (105), we hypothesized that mean PA level would decrease throughout the day, from morning to afternoon to evening. The comparison of the different splitting approaches was exploratory since no earlier comparisons were available in the literature.

II. Based on previous findings from Nunes and colleagues (162), we hypothesized that sleep parameters would indicate poor sleep quality (mainly a low SE, defined as a SE < 84%) in our convenient sample of COPD patients,

III. Based on the existing literature (149), we hypothesized that there would be a significantly positive association between daytime PA level and sleep quality in our sample of COPD patients.

Chapter IV

4.0 Article: Physical Activity and Sleep in Chronic Obstructive Pulmonary Disease (COPD)

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4.1 Abstract

Background: Extensive evidence has documented reduced physical activity (PA) levels, duration, and intensity in COPD patients compared to healthy controls. In return, diurnal PA patterns have rarely been studied. Better understanding diurnal PA patterns could help optimize interventions targeting PA levels. Also, examining links between PA patterns and other lifestyle factors may provide valuable insight for an optimal self-management. Disturbed sleep is another common feature in COPD and one of the symptoms most frequently reported by patients. Recent evidence in poor sleepers has suggested a possible reciprocal relationship between PA and sleep. This relationship has not, to our knowledge, been investigated in COPD patients. The aims of the present study were: i) to characterize, in COPD patients, diurnal patterns of objectively assessed PA from morning to afternoon to evening using three data handling approaches (arbitrary, mealtime, equal tertiles); ii) to characterize objectively measured sleep quality in COPD; and iii) to explore the association between daily PA and sleep quality parameters in COPD.

Methods: Fourteen COPD patients (aged 71 ± 9 years) with mostly moderate COPD (FEV_1: 58 ± 13 % predicted) participated in the study. Daily PA and sleep characteristics (Sleep Onset Latency [SOL], Wake After Sleep Onset [WASO], Total Sleep Time [TST], Sleep Efficiency [SE%] and Fragmentation Index [FI]) were assessed via actigraphy for 7-consecutive days, 24 hours/day. Daily PA was computed from rise time to bedtime (except for the arbitrary approach), while sleep characteristics were computed from bedtime to rise time. Diurnal PA patterns were evaluated by breaking down daily PA into three portions using an arbitrary approach (8:00-12:00, 12:01-16:00, 16:01-20:00), a mealtime approach (wake time- lunchtime, lunchtime- suppertime, suppertime- bedtime) and an equal tertiles approach (1^{st} Tertile, 2^{nd} Tertile and 3^{rd} Tertile). The interaction effect of period of the day (morning, afternoon and evening) by handling approach (arbitrary, mealtime, and equal tertiles) on PA level was examined with two-way repeated-measures ANOVA using the General Linear Model. This was followed, if needed, by simple main effect tests (ANOVAs) of period of the day effect for each handling approach, and pairwise comparisons with Bonferroni corrections to compare PA levels between different periods of the day. Associations between mean 7-day/night sleep parameters and i) daily PA levels, ii) PA levels in each tertile of the day, and iii) inter-tertile standard

deviation (SD) of PA level (as a measure of daily PA variability) were assessed with Pearson's or Spearman's correlations, depending on data distribution and sample size.

Results: There was a significant interaction effect of period of the day by handling approach on PA level ($F_{2.77, 36.03} = 18.01$, $p < 0.001$). Regardless of the data handling approach, a significant difference in activity count was observed between the different portions of the day, mean PA levels particularly dropping in the evening ($F_{2, 26} = 6.63$, $p < 0.005$ for the arbitrary split, $F_{2, 26} = 23.06$, $p < 0.001$ for the mealtime split, $F_{2, 26} = 22.16$, $p < 0.001$ for tertile split). This observation was homogeneous across our sample, but less evident with the arbitrary approach. Participants had, on average, a SOL of 22 ± 17min, WASO of 65 ± 29 min, TST of 383 ± 59 min, SE of 79 ± 9 % and FI of 45 ± 23 %. Sleep quality parameters showed very weak to weak associations with mean daily PA, very weak to moderate associations with PA in each portion of the day, and weak to strong associations with daily PA variability (correlation coefficients ranging from -0.50 to 0.42 across the different variables).

Conclusion: Results from this study support prior findings that PA levels decrease significantly in the evening compared to both morning and afternoon in COPD patients. They further suggest that the data handling approach used to evaluate diurnal PA patterns may affect the extent of the decrease observed. Based on the mean values obtained for SE, WASO, and SOL, some degree of sleep disturbances may be present, even in patients with moderate COPD. The association between PA and sleep quality parameters appears to be weak in this subset of patients compared to what was previously shown in "healthy" poor sleepers, but the PA-sleep relationship will have to be further investigated in COPD patients.

Key words: COPD, physical activity, diurnal patterns, accelerometer, sleep quality

4.2 Introduction

Chronic Obstructive Pulmonary Disease (COPD), is a preventable and manageable chronic lung disease characterized by partially irreversible obstruction and/or inflammation of the airways (11, 20, 51). It encompasses a cluster of respiratory diseases, which include mainly chronic bronchitis and emphysema(51). As a result of either process, the ability to breathe normally is decreased due to obstructed airflow related to excessive mucosal secretion and inflammation, the loss of elasticity of the bronchioles and alveoli, and/or damaged lung tissue (28). The progression of COPD often follows a downward spiral, which begins with airflow limitation and dyspnea, followed by inactivity and muscular deconditioning, leading to a worsening of the dyspnea sensation and eventually to invalidity and poor quality of life.

Levels of daily physical activity (PA) have been shown to drop substantially with age among the healthy elderly population, particularly after the age of 74 years (57). The decrease in PA levels becomes a more serious situation in COPD patients, as it has been shown that inactivity worsens their physical condition and may further increase their sensation of dyspnea (163, 164); however, it is not clear to what degree inactivity affects the progression of COPD (57). Physical inactivity is directly associated with patient's perception of dyspnea (58), and the sensation of dyspnea is disproportionally greater with decreases in lung function in inactive patients compared to active patients(58). Due to its significant impact on patients' physical condition and symptom perception, PA has become a valued outcome measure in COPD patients.

In the past decades, a vast body of evidence has suggested that levels (90-94), duration (95-102, 165) and intensity (95, 96, 98, 99, 102, 104, 105) of PA, as well as overall activity counts (92, 93, 97, 100, 102, 106) are significantly decreased in COPD patients compared to healthy subjects, which in most cases were matched for age, sex and body mass index (BMI). Much less studied, diurnal patterns of PA (i.e. time-of-day evolution of PA) may also warrant some consideration in COPD patients. Within-day variations in lung function parameters (FEV_1 and FVC), respiratory muscle strength (113), symptom perception (114), and response to symptom-limited incremental cardiopulmonary exercise testing (115) have been documented in COPD patients. While some parameters (e.g., symptom perception) appear to be worse in the morning,

others (e.g., pulmonary function, exercise response) seem to rather dip in the afternoon or evening, at least in certain subsets of patients (113-115). In a relatively recent study, Tabak et al. (105) documented a significant decrease in PA throughout the day from morning to afternoon to evening, particularly in unemployed COPD patients (n = 32). Employed COPD patients (n = 7) and unemployed healthy controls (n = 10) displayed a similar pattern, but the drop in PA was not statistically significant in those subgroups, possibly because of their small sample size. In return, employed healthy controls (n = 11) exhibited a different "A-shape" pattern, where PA peaked in the afternoon and was similar between morning and evening.

To our knowledge, Tabak et al.'s study (105) is the only one available to date on diurnal PA patterns in COPD patients. There is also a paucity of literature on this topic in the general population, young and old (112). Therefore, the significance of various diurnal patterns of PA is not known. In COPD patients, equally distributing daily PA is believed to improve their management. Indeed, COPD patients are advised by healthcare professionals to balance their energy expenditure throughout the day by alternating heavy and light activities (105). Yet, there is no PA literature to support this recommendation. Better understanding diurnal PA patterns in COPD patients could thus help optimize interventions targeting PA levels in this patient population. In this respect, Tabak and colleagues (105) made a landmark contribution to the COPD literature with their study. Nevertheless, two methodological limitations related to PA monitoring may have affected their findings.

First, the monitoring window in their study was relatively short (three-four days), and there was no mention of the respective contribution of weekend and weekdays. PA monitoring guidelines suggest a minimum of three-four days of monitoring with one weekend day to reach at least 80% of reliability; however, seven days of monitoring is preferred, as it represents the full week and allows for at least 90% of reliability (117). Another limitation of their study was the data handling approach used to determine onset, offset and splitting of the days. Indeed, an arbitrary handling approach was used, where day onset was fixed at 8:00, day offset was fixed at 20:00, and morning/afternoon/evening went from 8:00 – 13:00, 13:00 – 17:00, and 17:00 – 20:00, respectively. This was the case for all participants, regardless of their individual daily routines. Hours outside the 8:00 – 20:00 window during which participants were awake were therefore excluded, and the different portions of the day were unequal in time and not

representative of any particular event (e.g., meals). Additional research is warranted to further examine diurnal PA patterns in COPD patients using more empirical and ecological data handling approaches. Also, examining the link between PA patterns and other lifestyle factors may provide valuable insight for an optimal self-management.

Disturbed sleep is another common feature in COPD patients (124, 133) and it is one of the most frequently reported symptoms in this patient population (125). It has been suggested that around 40% of COPD patients report disturbed sleep (134, 166) and that a majority of patients have a sleep efficiency (SE) ranging from 50 to 70% (125), versus 84 % or more in healthy older adults (167, 168). Additionally, COPD patients are known to have difficulty falling and/or staying asleep, more light sleep and less deep sleep (REM), increased micro arousals, and recurrent shift between sleep stages (125). COPD patients exhibit diverse sleep disorders, such as insomnia and obstructive sleep apnea, and sleep-related disturbances, such as sleep-related hypoxemia, sleep hypoventilation, and restless leg syndrome (135).

Both PA and sleep are important health-related lifestyle factors that demonstrate significant decrease with age, but remain modifiable well into later life (144). More recently, evidence has suggested a possible reciprocal relationship between these two lifestyle factors (145-148). Positive associations between exercise training and both objectively (polysomnography, PSG) and subjectively (self report) measured sleep quality have been documented in individuals with poor sleep (150, 151). Furthermore, habitual PA has been associated with lower prevalence and incidence of insomnia, and more precisely with an improved ability to stay asleep in healthy elderly adults (146). In COPD patients, one study documented a significant inverse correlation between functional exercise capacity (as measured by the six-minute walk test) and subjective sleep quality (157). Yet, to our knowledge, the relationship between habitual PA and sleep has never been investigated in this patient population.

The aim of this project was to examine habitual PA and sleep in COPD patients and explore the potential association between these two lifestyle factors. More specifically, our objectives were: i) to characterize, in COPD patients, diurnal patterns of objectively assessed PA from morning to afternoon to evening using three different splitting approaches (arbitrary, mealtime,

equal tertiles); ii) to characterize objectively measured sleep quality in COPD; and iii) to explore the association between daily PA and sleep quality parameters in COPD.

4.3 Methodology

4.3.1 Study Design and Participants

This study is a secondary analysis of data collected during an observational prospective pilot project on *The Impact Of Time-Of-Day On The Acute Response To Incremental Exercise In COPD Patients* (169). The project was conducted between August 2010 and April 2011 in a convenience sample of 14 individuals with COPD recruited from Hôpital du Sacre Coeur de Montréal, in Quebec, Canada. Inclusion criteria were: 1) clinically stable COPD; 2) age ≥ 40 years; 3) smoking history ≥ 10 pack-years (20 cigarettes/pack); 4) a post-bronchodilator FEV_1 of less then 80% of the normal predicted value; 5) a ratio of FEV_1 over forced vital capacity (FVC) of less than 0.7; 6) previous experience of exercise testing. Exclusion criteria were: 1) a respiratory exacerbation in the past 4 weeks; 2) contraindications to exercise testing based on guidelines from the American Thoracic Society (4); 3) need for oxygen therapy; 4) any secondary condition other then COPD (e.g., asthma, severe arthritis, unstable coronary heart disease, left congestive heart failure, serious psychiatric comorbidity) that could affect measured outcomes; and 5) prescribed theophylline.

As part of the broader project, upon obtaining medical clearance for exercise testing, participants came to the research center for a total of four visits. During the first visit, demographics and clinical information such as age, sex, height, weight, and body mass index (BMI) were obtained and baseline spirometry was performed. During the same visit, subjects were also familiarized with the testing equipment and procedures. Visits 2-4 (each separated by > 36 hours) were meant to serve the abovementioned project on time-of-day variations in acute response to incremental exercise (170). Throughout the study, which lasted a minimum of 7 days and maximum of 14 days, participants were instructed to wear the Actiwatch on their non-dominant wrist every day, 24 hours/day. They were asked to keep the device free of clothing and to remove it while taking a shower or swimming, and when participating in activities that involved contact. Subjects were also asked to respect 8 hours of sleep per night during the

monitoring period and to press the event marker button on the watch to mark bedtime and rise time. For the duration of the study, subjects also completed a journal of their physical activity, meal times, sleep habits, and mood.

4.3.2 Assessments

4.3.2.1 Pulmonary Function Test

Baseline pulmonary function measures were obtained from the spirometry conducted during Visit 1, which was performed according to recommended techniques (171) . Predicted normal values from the European Community for Coal and Steel/ European Respiratory Society were used for comparison of obtained values to reference values (171).

4.3.2.2 Actigraphy

Hardware

The Actiwatch (Actiwatch- 2, Respironics, Bend, USA) is a wristband accelerometer with an activity sensor consisting of a miniature piezo-electric transducer (172). The activity sensor produces a voltage, which is then amplified, digitized, and recorded as an activity count (172) shown to be both reliable and valid in its measurements (170). The device is also equipped with a light-sensor. The Actiwatch is light (16g with the band, 43 x 23 x 10mm) and measures activity in all dimensions. The device has a sensitivity of 0.025 g-force (g) (at 2 count level) with peak values between 0.5-2g, a sampling rate of 32 Hertz, and a bandwidth of 0.32-7.5 Hertz. It is most often used for sleep/wake analysis; therefore consistency of the activity count at the low end (lower then 100 counts) is very good (172). It thus seems suitable for COPD patients who are typically older and more sedentary than healthy population. Additionally, Actiwatch has been validated for sleep assessment against PSG in young and older subjects, healthy and chronic primary insomniac patients, with overall high sensitivity (0.965) and accuracy (0.863), but low specificity (0.329) (129).

Software

The actigraphy data were analyzed with the Actiware software version 6.01 (MA, USA). The software identifies each epoch as sleep/wake using mathematical algorithm developed previously (173). Different wake thresholds can be set in order to score an epoch as sleep or wake. Epochs with activity counts equal or bellow the chosen thresholds are considered as sleep, while those with a count above the chosen threshold are considered as wake. The software threshold selections available are: i) low (20 counts per epoch; high sensitivity), ii) medium (40 counts per epoch; medium sensitivity), iii) high (80 counts per epoch; low sensitivity), and iv) automatic (i.e. computed automatically based on activity counts of the day). There are no specific recommendations by the manufacturer for different thresholds, but medium threshold is commonly used, such that this is what was applied in our study. The calculation for each 1 minute epoch is done according to the following formula: $A = (A'1)\left(\frac{1}{5}\right) + (A'2)\left(\frac{1}{25}\right) + AC + A2\left(\frac{1}{25}\right) + A1\left(\frac{1}{5}\right)$. $A'1$ and $A'2$ are the activity counts from prior 1-minute and 2-minute of the epoch being scored, and $A1$and $A2$ are the subsequent 1-minute and 2-minute, respectively. Figure 5 illustrates how this calculation is done.

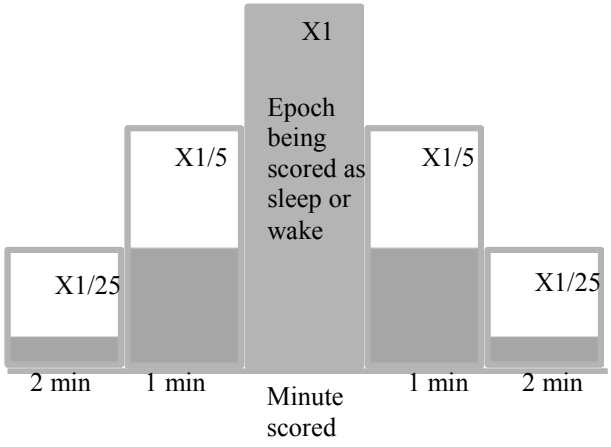


Figure 4 - Calculation to score a minute as wake or sleep

4.3.3 Data Handling

All data points were visually inspected for missing data. Bedtimes and wake times were determined empirically for each monitoring day. Figure 6 is a screen shot of an Actiwatch data

output. Each line is a 24-hour period with yellow sections representing time out of bed, blue sections representing time in bed, and black spikes representing activity epochs. Bedtime was determined by comparing bedtime markers against the information provided in the journal, and the activity count data. The investigator's marker was placed where two of the three methods best matched. Similar method was used to determine wake time. The small blue markers on Figure 6 show bedtime and rise time.

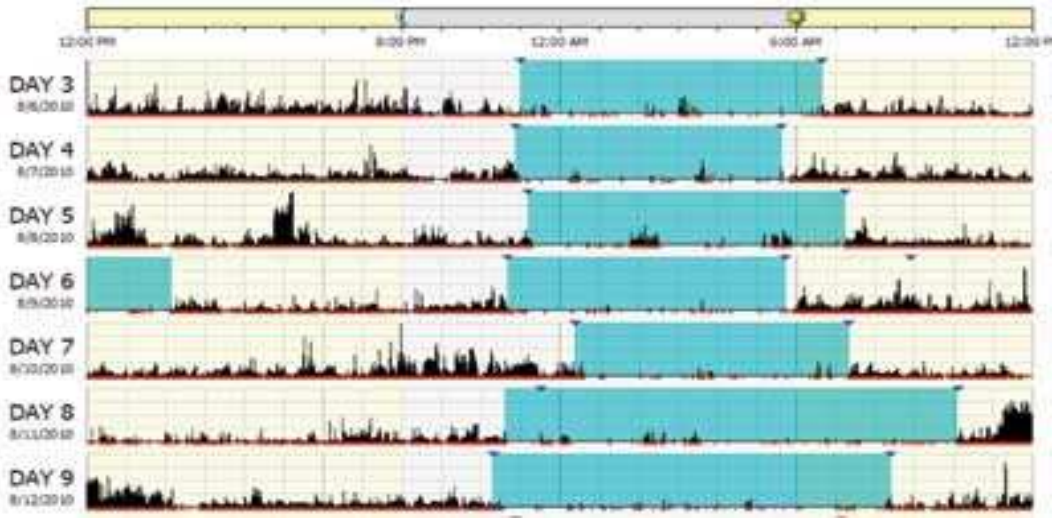


Figure 5 - Screen Shot of an Actiwatch-2 Output

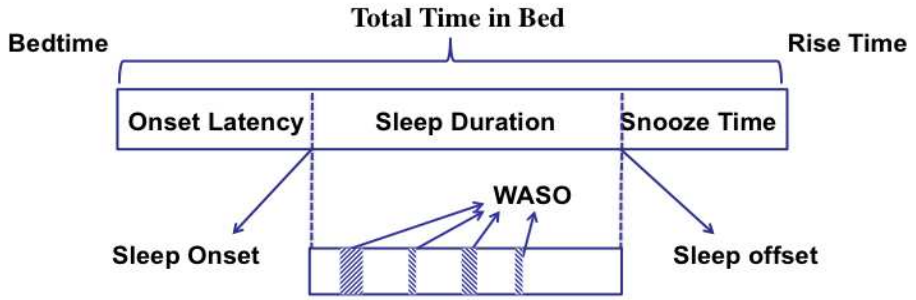
4.3.3.1 Data Handling for Physical Activity Measures

Physical activity data was analyzed from wake time to bedtime for seven consecutive valid days. Based on a systematic review article entitled "*A Catalogue of Rules*, *Variables, and Definitions Applied to Accelerometer Data in the National Health and Nutrition Examination Survey*" (174), the following set of rules were applied. Periods with more than 60 min of consecutive zeros were considered as non-wear time and excluded from analyses, in addition to non-wear time recorded in the participants' journals. A valid day was defined as a day with at least 10 hours of physical activity data. In addition, for the present study, if three or more consecutive hours of data were missing in a given day, the day was excluded from analyses. This was done to ensure sufficient representativeness of all parts of the day for analyses of diurnal PA patterns.

To address our first objective (characterization of diurnal PA patterns), valid days were split in three parts using three different approaches: 1) an arbitrary approach, as used in previous studies (105), in which daily PA was extracted from 8:00 to 20:00 and divided into morning (8:00-12:00), afternoon (12:01-16:00), and evening (16:01-20:00); 2) a mealtime approach, in which daily PA was extracted from rise time to bedtime and divided based on the meal times reported by participants in their journals (wake time to lunch time [WT-LT], lunch time to supper time [LT-ST] and supper time to bedtime [ST-BT]); and 3) a tertiles approach, in which daily PA was extracted from wake time to bedtime and divided into three equal tertiles (tertiles 1, 2, and 3, respectively).

4.3.3.2 Data Handling for Sleep Measures

Sleep characteristics were computed from bedtime to wake time for 7 consecutive valid nights. Nights with 180 minutes or more of consecutive zeros were excluded, as this time was considered non-wear time based on previous study (175). Sleep onset was determined by the software algorithm as the first 10 minutes of consecutive zeros after bedtime and labeled as the first sleep epoch. This process continued until the last epoch, which was labeled as sleep offset (or wake time). For our second objective (characterization of sleep), the following sleep quality parameters were calculated: (1) time in bed (TIB; period going from bedtime to the following wake time; 2) total sleep time (TST; total number of epochs between sleep onset and sleep offset or wake time scored as sleep by the software); 3) sleep onset latency (SOL; interval from bedtime to sleep onset in minutes); 4) sleep efficiency (SE; total sleep time/ time in bed X100); 5) fragmentation index (FI; measure of restlessness calculated from percent mobile and immobile bouts, with higher values signifying poor sleep continuity). Figure 7 summarizes computation of sleep characteristics.



Total Sleep Time (TST) = Sleep Duration – Wake After Sleep Onset (WASO)

Sleep Efficiency (SE%) = (Total Sleep Time/Total Time in Bed) X 100

Fragmentation Index (%)= (% mobile + % Immobile< 1min)/ % Immobile

Figure 6 - Computation of Sleep Characteristics

4.3.4 Statistical Analysis

The normality of the distribution of the studied outcomes was verified using measures of skewness and kurtosis. For our first objective, which was to characterize daily PA patterns according to three different handling approaches, descriptive analyses (mean ± standard deviation [SD]) were conducted for individual participants and for the group. Moreover, the interaction effect of periods of the day (independent variable #1 with three levels: morning, afternoon and evening) by handling approach (independent variable #2 with three levels: arbitrary, mealtimes, and equal tertiles) on PA level (dependent variable) was examined with two-way repeated-measures ANOVA using the General Linear Model. This was followed, if needed, by simple main effect tests (ANOVA) of the period of the day effect on PA level for each handling approach separately. Huynh-Feldt corrections for Sphericity were applied for analysis on more than two levels, but original degrees of freedom are reported. Pairwise comparisons with Bonferroni adjustment were then conducted in cases where a significant period of the day effect was detected with the ANOVA to identify between which levels the difference(s) in PA levels occurred. The effect size (Cohen's *f*) was calculated and interpreted according to the established methods (small: 0.1; medium: 0.25; large >0.4) (176).

For our second objective, which was to characterize sleep, descriptive analyses (mean ± standard deviation [SD]) were conducted for individual participants as well as for the group. For our third objective, which was to explore the relationship between daytime PA and sleep,

bivariate correlations were conducted between sleep parameters and daily PA, PA in each tertile of the day, and inter-tertile SD of PA using either Pearson r or Spearman rho, depending on the distribution of the data. Lastly, exploratory scatterplots were done to examine temporal relationship between daily PA and sleep parameters (SOL, WASO, TST, SE, and FI) for each monitoring day with its corresponding night for each participant. All statistical tests were two tailed and conducted at $p \leq 0.05$. The statistical analyses were performed with SPSS version 18.0 (Chicago, IL).

4.4 Results

Fourteen participants (9 men, 5 women) with moderate (n = 12) to severe (n = 2) airflow obstruction (FEV_1: 58 ± 13% of the normal predicted value, see appendix for FEV_1 distribution) completed the study. Upon examination of the age distribution, two distinct subgroups emerged as shown in Figure 8: a subgroup of younger-old participants aged 58-67 years and a subgroup of older-old participants aged 74-79 years. The younger-old subgroup consisted mostly of females (5/6) while the older-old subgroup was composed entirely of males (8/8). Given the documented impact of age on both PA and sleep (177, 178), this feature was considered in subsequent results. Baseline characteristics of the sample are presented in Table 2. Of note, only one participant had diagnosed obstructive sleep apnea and other participants had no diagnosed sleep disorder.

Figure 7 – Age distribution of the sample. Each marker represents one participant. Line and bar represent Mean ± SD

Table 2 - Baseline Characteristics of Sample and Age Subgroups

Characteristics	Full Samples	Younger-old	Older-old
n	14	6	8
Age (yr)	71 ± 7	64 ± 3	77 ± 2
Sex (male/female)	9/5	1/5	8/0
BMI (kg/m2)	27 ± 4	26 ± 5	27 ± 3
Smoking status (current, n)	2	1	1
FEV_1 (% Pred)	58 ± 13	56 ± 17	59 ± 10
FEV_1 /FVC (%)	53 ± 11	54 ± 9	52 ± 12
Wake Time	7:08 ± 0:46	6:45 ± 0:38	7:23 ± 0:47
Bedtime	22:51± 0:39	23:04 ± 0:38	22:41 ± 0:37
Sleep Efficiency (%)	79 ± 9	80 ± 9	76 ± 10
Daily PA (cpm)	250 ± 60	287 ± 64	222 ± 41

Values are Mean ± SD unless otherwise stated. BMI: body mass index; FEV_1: forced expiratory volume in 1sec; FVC: forced vital capacity; PA: physical activity, cpm: counts per minute.

4.4.1 Diurnal Physical Activity Pattern

Physical activity data were normally distributed. Table 3 presents PA levels for the different portions of the day according to the three splitting approaches. There was a significant interaction effect of period of the day (morning, afternoon and evening) by handling approach (arbitrary, mealtime, and equal tertiles) on PA level ($F_{2.77,\ 36.03} = 18.01$, $p < 0.001$). Follow-up ANOVAs indicated a significant difference in activity count between the different portions of the day regardless of the splitting approach ($F_{2,\ 26} = 6.63$, $p < 0.005$ for the arbitrary split, $F_{2,\ 26} = 23.06$, $p < 0.001$ for the mealtime split, $F_{2,\ 26} = 22.16$, $p < 0.001$ for tertile split) and large effect sizes ($f = 0.45$, 0.83, and 0.74 for the three approaches, respectively). For the arbitrary split, pairwise comparisons further revealed that the decrease was significant between morning and evening only ($p < 0.05$) and not between morning and afternoon ($p = 0.204$) or afternoon and evening ($p = 0.148$). For both mealtime and tertile split, pairwise comparisons showed that the difference in PA levels was significant between the first and third portions of the day ($p < 0.001$) and between second and third portions ($p < 0.05$), but not between first and second portions ($p = 1.0$). Since results for mealtime and equal tertiles splits were very similar, further results are shown for the equal tertiles split only.

Table 3 - PA Levels (Mean ± SD) for Different Portions of the Day According to Three Splitting Approaches

Arbitrary Split	
Morning (8:00-12:00)	301 ± 92
Afternoon (12:01-16:00)	277 ± 84
Evening (16:01-20:00)	238 ± 58*
Mealtimes	
WT-to-LT (7:08-12:25)	293 ± 76
LT-to ST (12:26-16:59)	280 ± 85
ST-to-BT (17:00-22:51)	165 ± 59**
Equal Tertiles	
1st Tertile (7:08-12:22)	288 ± 75
2nd Tertile (12:23-17:37)	285 ± 90
3rd Tertile (17:38-22:51)	176 ± 51**

WT: wake time; LT: lunchtime; ST: suppertime; BT: bedtime. *$p < 0.05$ vs morning PA, **$p < 0.001$ vs morning and afternoon PA.

Table 4 presents mean 7-day count for daily PA and for each tertile of the day, as well as inter-tertile SD (as a measure of variability) for each of the 14 participants. The two most active individuals are in blue; they also had the highest inter-tertile SD of the group. The two least active individuals are in red. Figure 9 illustrates diurnal PA pattern for individual participant and the mean for each age subgroup. As can be seen in both Table 4 and Figure 9, the decrease in mean PA level from the 1st tertile to the 3rd tertile was observable in all 14 participants. Likewise, the decrease in PA from the 2nd tertile to the 3rd tertile was present in all but one participant (ED1013).

Table 4 - Individual Data for 7-day PA Level (Daily and Per Tertile) and Inter-Tertile SD

Subjects ID	Daily PA	1st Tertile (7:08-12:22)	2nd Tertile (12:23-17:37)	3rd Tertile (17:38-22:51)	Inter-Tertile SD
ED001	182	234	188	126	54
ED002	214	230	249	174	39
ED003	215	293	197	160	68
ED004	186	185	223	147	38
ED005	251	322	281	151	89
ED007	349	444	480	117	200
ED008	303	362	355	185	100
ED010	228	231	269	183	43
ED011	371	404	453	248	107
ED012	257	288	258	223	32
ED013	287	316	252	293	33
ED015	249	252	298	195	51
ED017	174	219	188	119	51
ED018	235	256	300	142	82

Red: least active individuals, Blue: most active individuals

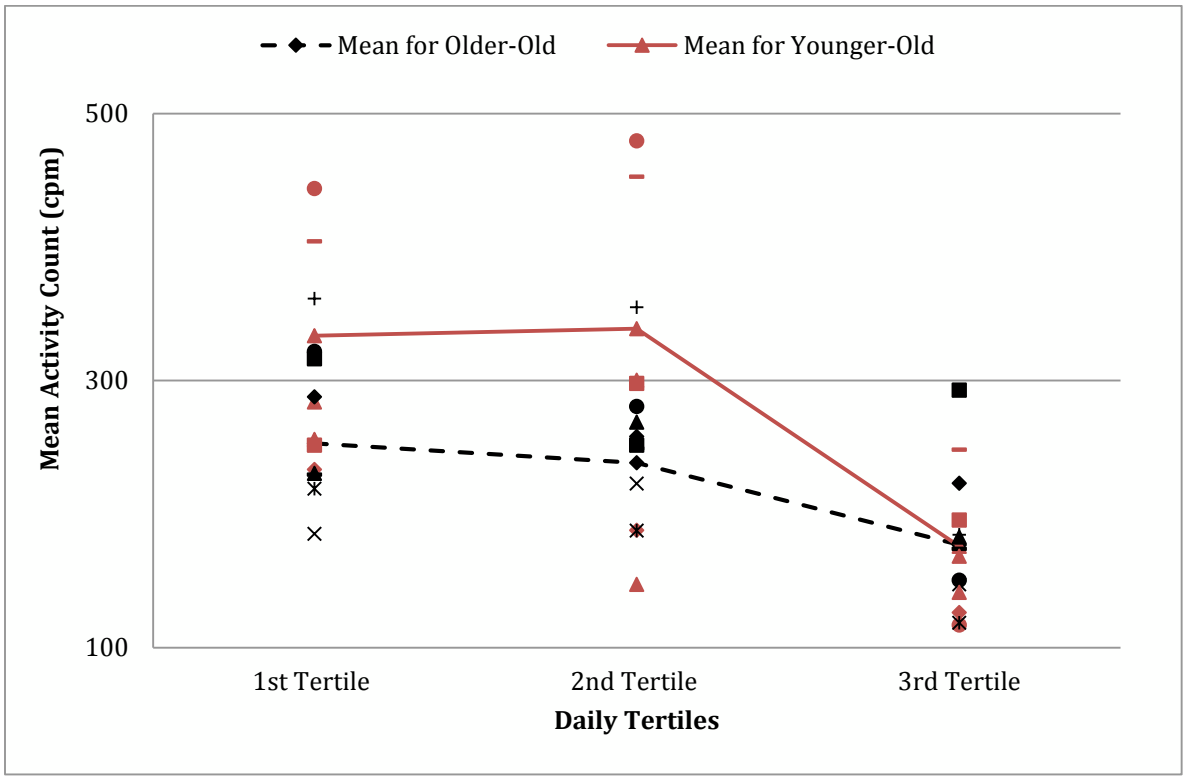


Figure 8 - Mean 7-day activity count for the 1st tertile (7:08-12:22), 2nd tertile (12:23-17:37) and 3rd tertile (17:38-10:51). Each subject is identified by a specific symbol, and each subgroup by specific colour (red: younger-old subgroup; black: older-old subgroup). Group means are represented by the solid red line and dashed black line, respectively.

4.4.2 Sleep Parameters

All sleep data were normally distributed. Descriptive results for extracted sleep parameters are presented for the full sample and both age subgroups in Table 5.

Table 5 - Sleep Characteristics (Mean ± SD) Over the 7-Night Period

Sleep Variables	Full Sample	Younger-old	Older-old
Time in bed (min)	483 ± 47	459 ± 45	503 ± 39
SOL (min)	22 ± 17	34 ± 37	23 ± 21
WASO (min)	65 ± 29	43 ± 14	81 ± 26
TST (min)	383 ± 59	370 ± 63	386 ± 65
Sleep Efficiency %	79 ± 9	80 ± 9	76 ± 10
Fragmentation index (%%)	45 ± 23	30 ± 8	56 ± 25

SOL: sleep onset latency, WASO: wake after sleep onset, TST: total sleep time

Table 6 presents individual data for 7-night sleep parameters (TIB, SOL, WASO, TST, SE and FI). The two individuals with the highest SE are in blue, while those with the lowest SE are in red

Table 6 - Individual Data (Mean ± SD) for 7 Night Sleep Parameters

Subjects ID	TIB (min)	SOL (min)	WASO (min)	TST (min)	SE%	FI (%%)
ED001	510 ± 64	8 ± 7	68 ± 17	416 ± 63	81 ± 4	42 ± 7
ED002	557 ± 69	36 ± 29	74 ± 25	429 ± 79	77 ± 6	55 ± 15
ED003	455 ± 64	30 ± 36	39 ± 11	377 ± 61	83 ± 8	24 ± 7
ED004	514 ± 39	7 ± 5	51 ± 18	447 ± 31	87 ± 3	37 ± 7
ED005	470 ± 86	58 ± 57	108 ± 47	300 ± 102	62 ± 10	92 ± 13
ED007	504 ± 22	2 ± 1	22 ± 7	475 ± 27	94 ± 2	20 ± 7
ED008	422 ± 72	23 ± 24	55 ± 24	332 ± 64	78 ± 3	23 ± 9
ED010	429 ± 90	12 ± 19	113 ± 70	284 ± 41	68 ± 12	73 ± 20
ED011	329 ± 53	23 ± 25	52 ± 16	312 ± 38	80 ± 5	40 ± 8
ED012	528 ± 56	48 ± 34	104 ± 37	355 ± 41	68 ± 9	81 ± 14
ED013	524 ± 52	8 ± 7	87 ± 11	423 ± 48	81 ± 2	50 ± 8
ED015	501 ± 90	35 ± 31	59 ± 33	406 ± 75	81 ± 6	40 ± 16
ED017	494 ± 51	6 ± 3	43 ± 17	436 ± 48	88 ± 3	17 ± 5
ED018	457 ± 37	17 ± 17	36 ± 8	378 ± 28	83 ± 4	30 ± 14

TIB: Time in Bed, SOL: Sleep Onset Latency, SE: Sleep Efficiency, WASO: wake after sleep onset, TST, total sleep time, FI: Fragmentation Index. Red: individuals with lowest SE, Blue: individuals with highest SE

4.4.3 Correlation between Physical Activity and Sleep

Table 7 contains correlations results between PA and sleep variables. There were no statistically significant correlations between mean 7-day PA or PA in each tertile of the day with any of the sleep parameters (SE, WASO, SOL, and FI). Correlation coefficients ranged from -0.50 to 0.42. For daily PA, the strongest correlation observed was with TST (r = -0.23, p = 0.43), while PA in each tertile of the day as well as inter-tertile SD most strongly associated with WASO (r = -0.23, p = 0.43 for tertile 1; r = -0.29, p = 0.31 for tertile 2; r = 0.42, p = 0.13 for tertile 3; r = - 0.50, p = 0.07 for inter-tertile SD). Figure 10 depicts scatterplots of WASO over PA in each tertile (panels A to C) and inter-tertile SD (panel D) for all 14 participants.

Table 7 - Correlation between PA variables (daily PA, PA in each tertile, and inter-tertile SD) with sleep parameters

PA pattern	Statistic	SOL	SE	WASO	TST	FI
Daily PA	Pearson r	0.05	0.05	-0.13	-0.23	-0.05
	p	0.88	0.87	0.66	0.43	0.87
1st Tertile	Pearson r	0.06	0.11	-0.23	-0.16	-0.13
	p	0.85	0.70	0.43	0.59	0.66
2nd Tertile	Pearson r	-0.05	0.18	-0.29	-0.14	-0.15
	p	0.86	0.55	0.31	0.65	0.60
3rd Tertile	Pearson r	0.20	-0.32	0.42	-0.31	0.32
	p	0.49	0.26	0.13	0.29	0.27
Inter-tertile SD	Spearman r	-0.11	0.20	-0.50	-0.18	-0.49
	p	0.71	0.48	0.07	0.53	0.08

SOL: sleep onset latency, SE: sleep efficiency, WASO: wake after sleep onset, TST: total sleep time, and FI Fragmentation index

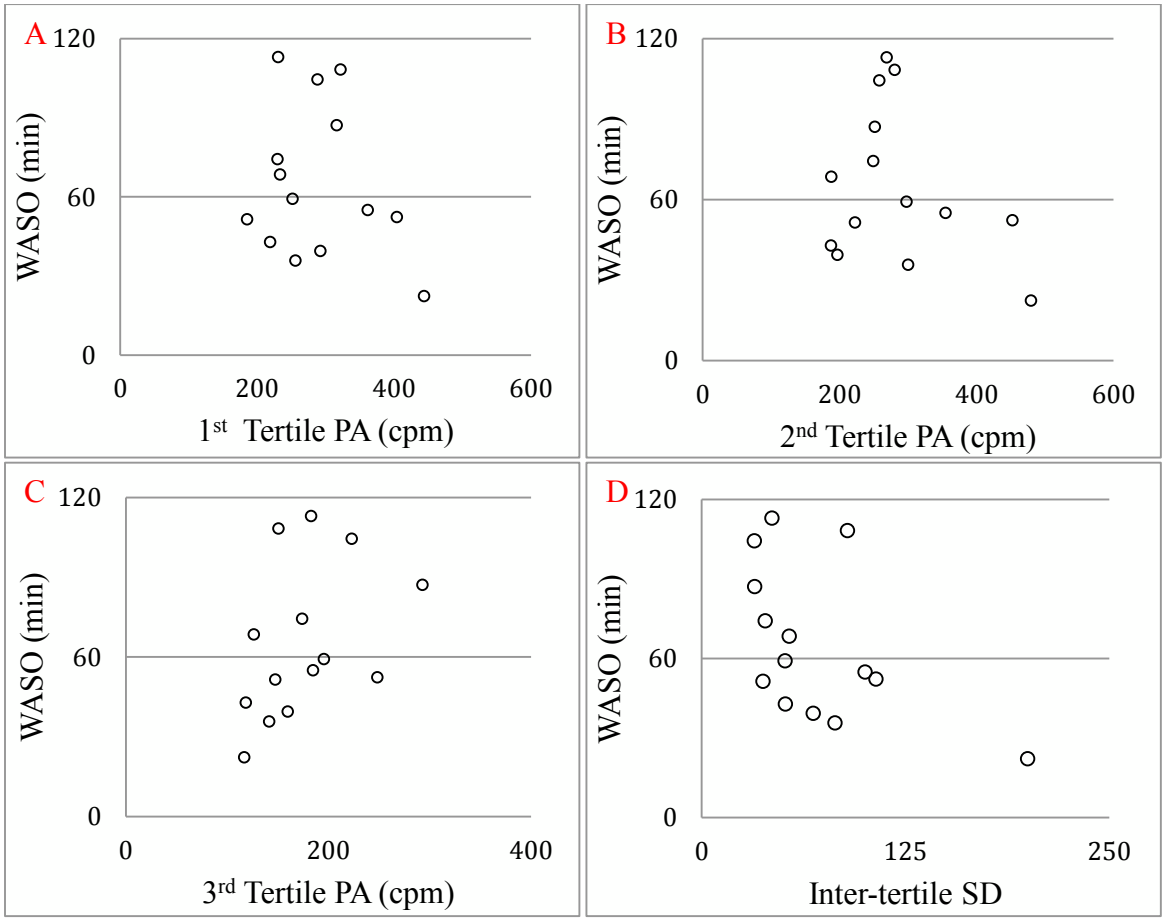


Figure 9 – Scatterplots of WASO and PA in each tertile of the day (panels A to C) and inter-tertile SD (panel D)

Tables 8 and 9 display correlations results for the younger-old and older-old subgroups, respectively. While results were similar for both subgroups for certain associations (across the 3rd tertile for example), some evident disparities were noted between the two subgroups, particularly in the 2nd tertile of the day.

Table 8- Association between PA variables with sleep parameters for younger-old subgroup

	Test	SOL	SE	WASO	TST	FI
Daily PA	Spearman's r	0.37	-0.26	-0.09	0.20	-0.37
	p	0.47	0.62	0.87	0.70	0.49
1st Tertile	Spearman's r	-0.49	0.14	-0.49	-0.09	-0.66
	p	0.33	0.78	0.33	0.87	0.156
2nd Tertile	Spearman's r	-0.77	0.54	-0.37	0.20	-0.43
	p	0.07	0.27	0.49	0.70	0.40
3rd Tertile	Spearman's r	0.60	-0.49	0.83	-0.60	0.71
	p	0.21	0.33	0.04	0.21	0.11

SOL: sleep onset latency, SE: sleep efficiency, WASO wake after sleep onset, TST: total sleep time & FI: fragmentation index.

Table 9- Association between PA variables and sleep parameters in Older-old subgroup

	Test	SOL	SE	WASO	TST	FI
Daily PA	Spearman's r	0.48	-0.48	0.48	-0.38	0.50
	p	0.23	0.23	0.23	0.35	0.21
1st Tertile	Spearman's r	0.69	-0.67	0.67	-0.69	.71
	p	0.06	0.07	0.07	0.06	0.05
2nd Tertile	Spearman's r	0.86	-0.95	0.95	-0.79	0.93
	p	0.01	0.00	0.00	0.02	0.00
3rd Tertile	Spearman's r	0.57	-0.57	0.69	-0.43	0.60
	p	0.14	0.14	0.06	0.29	0.12

SOL: sleep onset latency, SE: sleep efficiency, WASO wake after sleep onset, TST: total sleep time & FI: fragmentation index.

Figure 11 (panels A to D) illustrates scatterplots of daily PA and corresponding night sleep parameters (each data point) for the 7 monitoring days for each of the 14 participants (specific symbol per participant). No specific temporal association between daily PA and sleep parameters was identified.

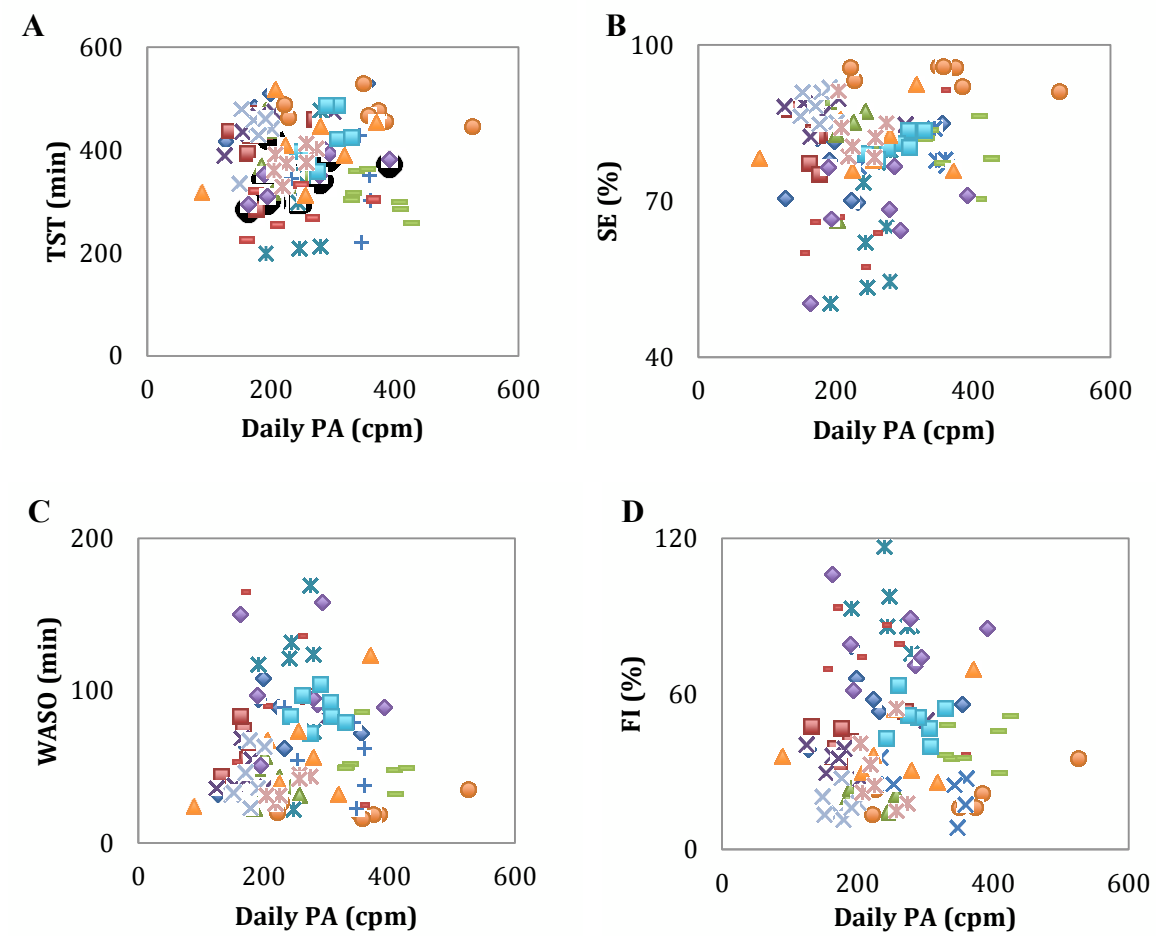


Figure 10 - Mean daily activity and corresponding night sleep parameters (each marker) for al 14 participants **(specific symbol per participant). TST: total sleep time, SE: sleep efficiency, WASO: wake after sleep onset, FI: fragmentation index.**

4.5 Discussion

4.5.1 Diurnal Physical Activity Patterns

The first objective of the study was to describe diurnal patterns of PA in COPD patients. It was hypothesised that PA levels would decrease throughout the day. Our findings support this hypothesis, but more precisely suggest that mean PA levels drop particularly in the evening. This observation was highly homogeneous across our sample, with evening PA being less than morning PA in 14/14 patients and less than afternoon PA in 13/14 patients. Our study participants, who were conveniently sampled, unexpectedly formed two distinct age subgroups, which were characterized a posteriori as younger-old (57-67 years, mean = 64 years) and older-old (74-79 years, mean = 77 years) patients. Although younger-old patients displayed higher PA levels in the morning and afternoon compared to their older-old counterparts, both subgroups fell to similar low levels of PA in the evening (Figure 9).

In the literature, studies examining diurnal PA patterns are scarce, both in the general population and in COPD patients. One study conducted in an elderly healthy population (mean age = 73 ± 3 years) showed that participants were mostly active from 6 to17h and that activity levels then decreased in the evening (116). In COPD patients, to our knowledge, only one study by Tabak et al. (105) evaluated diurnal patterns of PA. They too reported a significant decrease in activity levels from the morning (8-13h) and afternoon (13-13h) to the evening (17-20h) in unemployed COPD patients (n = 32). They also observed the same pattern, but not statistically significant, in employed COPD patients (n = 7) and unemployed healthy controls (n = 10). Conversely, in employed healthy controls (n = 11), they reported an "A-shape" pattern, where PA levels peaked in the afternoon, but were similar between morning and evening (105). Of note, the healthy control group in Tabak et al.'s study (105) was significantly younger than the COPD group. Overall, it is therefore difficult at this point in time to delineate the role of COPD per se versus factors associated with the disease (age, employment, etc.) on diurnal PA patterns. The suggested link between employment status and PA levels/patterns warrants replication in larger samples of employed and unemployed COPD patients and age-matched healthy controls.

As part of our first objective, we also explored PA patterns according to three different data handling approaches: an arbitrary, a mealtime, and an equal tertiles splitting approach. The arbitrary split, based on prior studies (105), considered only 12 hours of the day, from 8:00 to 20:00, while the other two methods considered the full window of hours between wake time and bedtime. Regardless of the splitting approach, PA levels decreased significantly in the evening, but the extent of the decrease, which was similar between mealtime and equal tertiles splits, was less with the arbitrary approach. Given that diurnal PA patterns have not been examined much in any population, there are no guidelines as to which approach should be favoured. Studies in other chronic conditions (chronic lower back pain (112) and chronic fatigue syndrome (179)) have used arbitrary approaches (e.g., 8:00-12:00, 12:00-18:00 and 18:00-22:00), similar to Tabak and colleagues (105) in their study in COPD (8:00-13:00, 13:00-17:00 and 17:00-20:00).

An important issue with the arbitrary approach is that valuable data are missed in the morning (between actual wake time and the arbitrarily set day onset time, e.g. 8:00) and in the evening (between day offset time and actual bedtime). Since PA levels were reported in average counts per minute in the present study, decreasing the monitoring window (denominator) with the arbitrary approach resulted in an increased count for morning and evening PA (Table 3). Another issue with this approach is that splitting the day arbitrarily may not reflect patients' daily routines. Food intake, for example, is related to individual habits and social norms (180). Empirically setting day onset and offset with actual wake time and bedtime, and splitting the day according to self-reported meal times allows for a more ecological and individualized data extraction. However, it requires much more data handling and the completion of daily journals for meal times. The equal tertiles approach does not decrease data handling requirements, but removes the need for daily journals, which would be a valuable feature for large population studies. Another advantage of the equal tertiles approach is that each portion of the day contains the exact same number of hours. According to our findings, it results in similar morning, afternoon, and evening PA counts as the mealtime approach, thus potentially offering a compromise between the arbitrary and mealtime approaches.

4.5.2 Sleep Quality

The second objective of the study was to describe sleep quality in COPD patients, with the hypothesis that actigraphy-assessed sleep parameters would suggest poor sleep quality (particularly a reduced SE). Our study participants had, on average, a SE of 79 ± 9%, about one hour (65 ± 29 minutes) of WASO, over six hours (383 ± 59 minutes) of TST, and 22 ± 17 minutes of SOL. These findings are somewhat discrepant from earlier results from Nunes et al. (162) comparing actigraphy-measured sleep in COPD patient (n = 26) versus age-matched healthy controls (n = 15). In their study, COPD patients were reported to have a SE of 73%, 96 minutes of WASO, less than five hours (280 minutes) of TST, and 40 minutes of SOL; the corresponding numbers for their age-matched healthy controls were a SE of 87%, 49 minutes of WASO, six hours (360 minutes) of TST, and 11 minutes of SOL. Thus, patients who participated in the present study had relatively preserved sleep quality parameters compared to those who completed Nunes et al.'s (162) investigation. This is perhaps not surprising since our participants had predominantly moderate COPD, while theirs included severe and very severe patients. Nevertheless, the mean values obtained for SE, WASO, and SOL in the present study suggest some degree of sleep disturbance in a sample of patients with mostly moderate COPD, resembling or even surpassing what has been documented with actigraphy in older adults with insomnia (167).

Studies using polysomnography (PSG) to characterize sleep in COPD patients have also documented decreased SE (132, 181, 182). Hynninen et al. (182) reported impaired SE (< 85 %) in 57.5 % of the COPD patients who took part in their study. Similarly, Valipour et al. (132) documented significantly lower SE in COPD patients compared to healthy controls (SE: 75 ± 13% and 82 ± 11% for COPD and healthy controls, respectively). The causes of disturbed sleep in COPD patients are not yet fully understood, but seem to stem from a complex and multifactorial process, possibly due to one or more of the following factors: hypoxemia, hypercapnia, physiological changes associated with sleep, inflammation, COPD medications, and/or nicotine use (135). Furthermore, COPD is commonly diagnosed later in life, in middle- or old-age adults, and in individuals who are mostly long-term smokers and who often suffer from comorbidities associated with smoking and /or old age. In the general population, it is well documented that the frequency of disturbed sleep (especially decreased SE) increases with age;

this is also likely true for COPD patients. In the present study, the older-old subgroup showed lower SE and higher WASO and FI compared to the younger-old subgroup, which is typical of the aging effect on sleep. In return, the older-old subgroup had lower SOL and higher TST compared to the younger-old subgroup. Sex may have influenced this later observation since the older-old subgroup was entirely composed of males, while the younger-old subgroup consisted predominantly (83%) of females, and sex differences in sleep quality in favour of males have been previously noted (183). Additional studies with larger sample sizes and consideration of age and sex will be needed to further characterize sleep quality in COPD patients in an ecological setting.

4.5.3 Correlation between Physical Activity and Sleep

The third objective of our study was to explore the association between daily PA and sleep quality parameters in COPD patients, with the hypothesis that there would be a positive relationship between these two health behaviours. Our findings generally suggest very weak to weak correlations between mean daily PA counts and sleep quality parameters. When PA was broken down into tertiles of the day, and when inter-tertile SD (a measure of within-day variability in PA) was considered, stronger correlation coefficients with sleep parameters were observed. Of the sleep parameters assessed in the present study, WASO showed the strongest associations with PA in each tertile of the day and inter-tertile SD. Furthermore, within-subject examination of temporal (day with corresponding night) associations between PA and sleep parameters discerned no identifiable pattern.

Very few studies have examined the relationship between PA and sleep using objective measurements of both variables. In COPD patients, to our knowledge, this is the first report of any type of association between habitual PA and sleep parameters. Our results regarding the weak correlations between mean daily PA and sleep parameters are in line with findings from Lambiase et al. (148), which documented no association between objectively measured average weakly PA and average weakly sleep parameters in older women. Additionally, another study by Youngstdt et al. (154) reported no association between daily PA and sleep parameters in healthy normal sleepers. Physical activity has been shown to be associated with sleep quality particularly in individuals with poor sleep (149). Participants in the present study had relatively preserved

sleep; this may explain the weak associations observed between PA and sleep parameters. Future trials investigating this relationship may want to target COPD patients with documented sleep disturbances. There are no prior studies which we know of that have examined the association between sleep parameters and PA in different parts of the day. Based on the present findings, future studies should consider breaking down daily PA into periods of the day and include a measure of within-day PA variability (e.g., inter-tertile SD) to examine the relationship with sleep.

Of note, our two age subgroups showed quite different patterns of associations between PA and sleep, particularly for the 2nd tertile of the day. Given the size of these subgroups (8 and 6), inferences should not be made based on these findings. However, they highlight the importance of considering age (and sex, as mentioned above) in future studies looking at PA and sleep, otherwise important associations may be overlooked. Although the relationship between PA and sleep across different age groups has not been precisely examined, it is well documented that age greatly influences both PA (184, 185) and sleep (178).

4.5.4 Clinical Implication

In the present study, a tri-axial accelerometer was used to describe diurnal patterns of PA and standard sleep quality parameters in COPD patient. Our results add to those of Tabak and colleagues (105) to provide a better understanding of within-day PA behaviour in COPD and may, in the long term, offer valuable insight for interventions targeting PA. Further, we compared three different data handling approaches for the evaluation of PA patterns: an arbitrary, mealtime, and equal tertiles approach. Our findings suggest that the equal tertiles approach may present a valuable option, particularly for large trials, since it seems to lead to similar counts as the ecological mealtime approach, but does not require the daily completion of a journal. For applications in large population studies, computer-programming algorithms should be considered for the determination of wake times and bedtimes and for the equal tertiles split, as it would reduce risk of errors and simplify data handling. Moreover, our results somewhat support previous findings of a reduced sleep quality in COPD patients, but highlight the need for additional research on the characterization of sleep quality in COPD patients in an ecological setting. Additionally, this study was the first to explore the association between PA and sleep

parameters in COPD patients. Our findings of an inverse association between within-day PA variability and parameters of "poor" sleep quality (WASO and FI) challenges the current recommendations to balance energy expenditure throughout the day (because as within-day PA variability increased, parameters of sleep fragmentation decreased). The results obtained may be helpful in generating hypotheses about this likely complex relationship.

4.5.5 Limitations

There are several limitations that should be taken into consideration in the interpretation of the present findings and for future studies on the subject. First, the sampling approach (convenience sampling) may have introduced a selection bias, thereby affecting the study's both internal and external validity. Likewise, the lack of a control group limits the internal validity. Even though levels of PA have been monitored objectively in COPD populations in previous studies, due to differences in the devices used to measure PA across studies, comparisons to prior findings is limited. Furthermore, this is only the second study on diurnal PA patterns in COPD patients, and the inclusion of a control group would have provided a better understanding of the influence of COPD per se on PA patterns within a day. Lastly, the small sample size limits the generalizability of the findings. Also due to the small sample size, it was not reasonably possible to control for potential covariates that may influence both PA and sleep (e.g., age, sex, BMI, etc).

4.5.6 Future Directions

Larger studies with age- and sex- matched healthy control groups will be needed to confirm, clarify, and/or further test our findings and put them into perspective with the general older adult population. A larger sample will allow for advanced statistical analyses with the ability to control for covariates if needed. It may also provide more variability in PA and sleep parameters, which would help detect patterns of association, if such patterns are present. Furthermore, having information on participants' employment status or, ideally, including employed and unemployed participants may be of importance in understanding diurnal PA patterns of COPD patients. Lastly, further exploring within-subject temporal associations between physical activity and sleep as well as examining their interactive effects on disease outcome and patient's quality of life in COPD patients seems warranted.

4.5.7 Conclusion

In summary, result from this study support prior findings that PA levels decrease significantly in the evening compared to both morning and afternoon in COPD patients. They further suggest that the data handling approach used to evaluate diurnal PA patterns may affect the extent of the decrease observed. The equal tertiles handling approach may offer a valuable compromise between the common arbitrary approach and the more ecological mealtime approach. Based on the mean values obtained for SE, WASO, and SOL in the present study, some degree of sleep disturbances may be present, even in patients with moderate COPD. The association between PA and sleep quality parameters appears to be generally weak in this subset of patients compared to what was previously shown in "healthy" poor sleepers, but the PA-sleep relationship will have to be further investigated in COPD patients.

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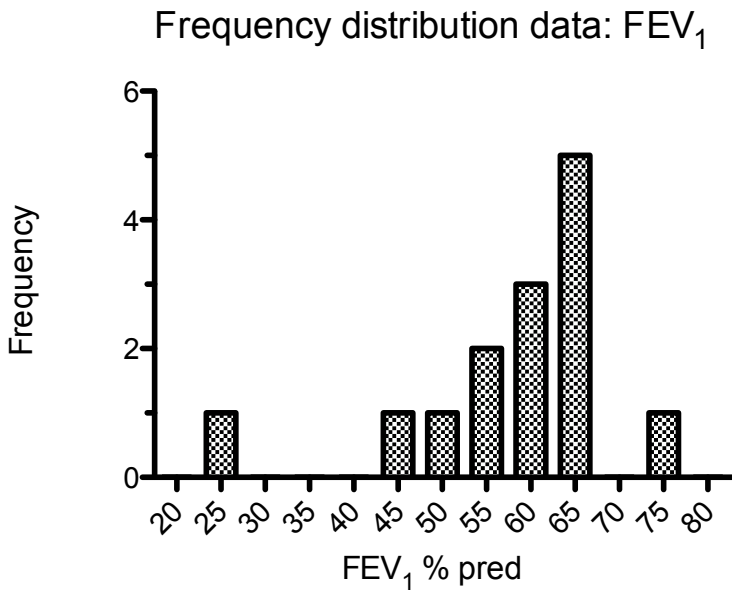
6.0 APPENDIX A: Frequency distrebution of disease severity measured by FEV_1



7.0 APPENDIX B: Manuscript - The Role of Sleep and Physical Activity on the Risk for Cardiovascular Disease

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Abstract

Sleep and physical activity are important health behaviors promoting cardiovascular health. Large bodies of literature have documented the direct effects of sleep and physical activity on risk factors for cardiovascular disease (CVD). This review aimed to highlight the interactive effect of sleep and physical activity on CVD risk. The extant literature suggests that sleep and physical activity are lifestyle behaviors that interact and act synergistically to influence CVD risk. Adopting healthy lifestyles encompassing both adequate sleep and regular physical activity is optimal to maintain cardiovascular health.

Keywords: Sleep, Physical activity, Sedentary behavior, Cardiovascular disease, Obesity, Metabolic syndrome, Diabetes, Cardiovascular events.

Introduction

Maintaining a healthy lifestyle encompassing adequate sleep and regular physical activity (PA) promotes optimal health over the life course. Both poor sleep and physical inactivity increase risk for several physical and mental diseases [1-3].

Sleep is an important modulator of cardiovascular function in both health and disease conditions. Sleep duration has been linked with cardiovascular disease (CVD) risk. Indeed, several studies have suggested a U-shape association between sleep duration and mortality, with 7 hours of sleep per day being associated with the lowest mortality, and shorter (6 or less) or longer (10 or more) sleeping time being associated with increased CVD mortality and morbidity [4-6]. Furthermore, the presence of certain sleep-related disturbances, such as obstructive sleep apnea, has been related to increased risk for the occurrence of cardiovascular events, such as myocardial infarction, coronary heart disease, heart failure, atherosclerosis, and ischemic stroke [7, 8], and to several CVD risk factors, such as obesity, hypertension, and diabetes [9, 10]. Insomnia is another risk factor for the development of CVD, such as coronary heart disease, and CVD risk factors such as hypertension, diabetes mellitus and metabolic dysregulation [11-13]. Periodic limb movements during sleep, another sleep-related disorder, has also been associated with greater risk for CVD [14]. Inadequate sleep resulting from behaviorally-induced shortened sleep or sleep disorders is thus a potential risk factor for CVD.

PA can be defined as any movement of the body generated by skeletal muscle contraction and resulting in increased energy expenditure [15]. Among healthy individuals, a dose-response relationship has been reported between PA and CVD risk, with highest levels of PA generally being linked with the greatest reduction in risk of CVD [16-18]. In individuals with stable coronary heart disease, an inverted J-shape association was recently documented, with patients reporting the lowest PA levels consistently having the highest hazards (for CVD events, CVD-related and all-cause mortality), but also those reporting daily strenuous PA showing an increased mortality risk [19]. In 1995, a joint collaboration between the Center for Disease Control and the American College of Sports Medicine (ACSM) led to the first official recommendation to accumulate 30 minutes or more of moderate PA on most, preferably all, days of the week [20]. In 2007, the ACSM and American Heart Association updated the

recommendations to clarify that individuals wanting to improve fitness, prevent disease and reduce weight may need to exceed the minimum recommendations of at least 150 minutes of moderate activity per week [21]. More recently, sedentary behavior (SB), such as extended sitting time, has emerged as a potential risk factor independent from PA [22]. In other words, an individual that meets the PA recommendations but spends a large fraction of time in sedentary activities would still be at an increased risk of CVD [23]. Therefore, simply meeting the activity recommendations may not be enough to mitigate the deleterious effects of SB on cardiovascular health.

The independent role of sleep and PA on CVD risk has thus been rather well documented, but how these two factors interact to affect CVD risk remains much less described. Therefore, the present review focuses on this potential interaction by summarizing recent literature investigating the interactive effect of sleep and PA on CVD risk, defined as the likelihood of having either a known CVD risk factor or a CVD event. In total, we reviewed 17 recent studies (i.e., published within the last 15 years), which were conducted in heterogeneous populations, belonging to different geographical areas, ethnicities, ages, or genders. Studies were grouped into two categories: i) those related to cardiovascular risk profile (13 studies), and ii) those related to cardiovascular events (4 studies). **Table 1** and **Table 2** summarize the main methodological information pertaining to the reviewed studies from both categories.

Sleep, Physical Activity, and Cardiovascular Risk Profile

Sleep, Physical Activity, and Obesity

Obesity is known to be a major risk factor for CVD and it is associated with increased mortality from CVD [24, 25]. Sleep, PA, and SB have each been shown to be independently associated with obesity in systematic reviews [26-28]. Only a few studies have examined sleep, PA, and SB together in relationship with obesity as the main outcome. In a cross-sectional study on Australian adults (N = 1 162), Di Milia et al. [29] looked at relationship between obesity defined as a body-mass index (BMI) $\geq$ 30 kg/m^2, calculated from self-reported height and weight values and self-reported sleep duration. They found that obesity was significantly associated with short sleep duration ($\leq$ 6 hours/day), and this association remained significant when adjusting for self-reported PA, SB, demographic variables and work-related factors. Less PA, and more SB

(i.e., extended sitting time) were also associated with obesity. However, being overweight (BMI = 25–29.99 kg/m^2) was not found associated with sleep duration, PA or SB. All variables in this study were obtained through self-reports and thus not verified objectively, which constitutes the main limitation of these findings.

Other studies have examined the effects of sleep, PA, and SB on objectively measured obesity markers. Vioque et al. [30] assessed the relationship between obesity and time spent in SB (i.e., watching TV) or sleeping, in a general adult Spanish population (N = 1 772, cross-sectional). Sleep, leisure-time PA (LTPA), and SB were self-reported, while obesity was assessed by objectively measured BMI. They reported that obese people spent more time watching TV and less time sleeping. Watching TV ≥ 4 hours/day or sleeping ≤ 6 hours/day were both associated with higher odds ratio of obesity, after adjusting for LTPA and demographic variables. This effect followed a dose-response relationship for both variables: each additional hour of TV watching increased the odds ratio of obesity by 30 %, while each additional hour of sleep decreased the same odds ratio by 24 %. In this study, LTPA level was not associated with risk for obesity.

In a large cross-sectional study, Forgelholm et al. [31] studied relationships between obesity, physical inactivity, sleep duration, and sleep-related disturbances (e.g., obstructive sleep apnea (OSA), insomnia-related symptoms concomitant with daytime tiredness) in 7 641 adults (> 30 years old) from the general population in Finland. Screening questionnaires were used to assess sleep duration, probable sleep-related disturbances, and LTPA. The presence of abdominal obesity and overall obesity was objectively verified by the measurement of waist circumference (WC) and BMI respectively. Physical inactivity and probable OSA were independently associated with abdominal obesity (WC ≥ 102 cm in men, WC ≥ 88 cm in women). In addition, longer sleep duration (≥ 9 hours/day) was associated with lower likelihood of abdominal overweight (WC: 94-101 cm), but only in men. The study also included analyses of inverse models looking at the predictors of sleep duration and sleep disturbances. It was found that physical inactivity was associated with shorter sleep duration (≤ 6 hours/day) and that abdominal obesity decreased the likelihood for long sleep times and increased the likelihood for short sleep times, in men only. This relationship between abdominal obesity and sleep durations remained significant when controlling for depression, PA, and age. This study overall illustrates the effects

of both PA and sleep on obesity, and the bidirectionality between those factors and CVD risk, suggesting a vicious circle among physical inactivity, poor sleep, and abdominal obesity.

While these previous studies were conducted on adult samples, some reports investigated the relationships between sleep, PA, SB, and obesity in adolescents. In a large cross-sectional study of 9 589 adolescents, Laurson et al. [32] investigated whether meeting healthy recommendations of sleep (≥ 8 hours/day), PA (≥ 1 hour/day) and SB (≤ 2 hours/day) influenced obesity as assessed by self-reported BMI. Youths that failed to meet healthy recommendations for any of the three behaviors were more likely to be obese. However, the effect of not meeting PA recommendations had a stronger influence on obesity than sleep or SB. They also showed that not meeting one recommendation increased odds of not meeting the two others, indicating the interdependent nature of these health behaviors. Furthermore, Garaulet et al. [33] assessed the association between short sleep duration and obesity in a large cross-sectional sample of European adolescents (N = 3 311). Sleep duration was estimated by a questionnaire, whereas PA and SB were assessed by both objective measure (i.e., accelerometry) and self-reported questionnaire. Objective morphometry measures (e.g., BMI, WC) were used to assess obesity. They showed that short sleep duration (< 8 hours/day) was associated with increased obesity markers. Interestingly, short sleep was also associated with increased SB (e.g., watching TV) and less adequate food habits, which suggests that the association between sleep and obesity was related to factors influencing both sides of the energy balance equation (i.e. energy consumption and expenditure).

Few longitudinal studies have examined both sleep duration and PA in relation to obesity. In a cross-sectional analysis of 537 healthy adults, Chaput et al. [47] reported that both short sleep duration (6 hours or less per day) and the absence of high intensity PA were associated with BMI. In the 6-year follow-up of 283 of these individuals, short sleep duration was associated with a 1.65 kg greater weight gain over the follow-up period, while the absence of high intensity PA was associated with a more modest increase in weight (1.23 kg) over time. Among individuals who were not obese at baseline, short sleep duration increased the risk of becoming obese, independently of PA [34]. Similarly, in the Nurses' Health Study, 68 183 women aged 39-65 provided information on sleep duration in 1984 and self-recorded their weight every two years for the next 16 years [35]. At baseline, women sleeping 5 hours or less

weighed on average 2.47 kg more than those who slept 7 hours and 1.24 kg more than those sleeping 6 hours or less. Importantly, shorter sleep duration was also associated with a greater weight gain during the 16-year follow-up. Over the following 10 years, women who slept 5 hours or less gained 0.73 kg and those sleeping 6 hours gained 0.26 kg more than did participants who slept 7 hours on average. Women who slept 5 hours of less were also 32 times more likely to experience a major weight gain of more than 15 kg during the follow-up than participants sleeping 7 hours. Importantly, the effect of sleep duration on weight gain was independent of PA [35].

Sleep, Physical Activity, and Metabolic Profile

Dyslipidemia (elevated low-density lipoprotein [LDL] cholesterol, reduced high-density lipoprotein [HDL] cholesterol, elevated total serum cholesterol, and/or elevated triglycerides), hypertension (elevated systolic and/or diastolic blood pressure [BP]), and a pre-diabetic state (impaired fasting glucose or impaired glucose tolerance) are well-recognized independent risk factors for CVD [36, 37]. Taken as a cluster which further includes abdominal obesity, these risk factors are sometimes referred to as the *metabolic syndrome*. There is no universally accepted definition for the metabolic syndrome, but criteria proposed by *NCEP ATPIII Guidelines* [38] and, more recently, by a *World Health Organization (WHO) Expert Consultation* [39] are commonly used. This clustering of metabolic factors is believed to be a stronger predictor of diabetes mellitus and CVD risk than the sum of individual factors [40], but its recognition as a distinct pathophysiology remains controversial [41]. Lifestyle behaviors influencing individual determinants of the metabolic syndrome are the same as for the syndrome itself and include sleep, PA/SB, smoking, and alcohol intake [42]. The following section presents findings from six studies, which have reported on the effects (independent and combined or interactive) of sleep duration and/or quality and PA and/or SB on metabolic risk factors, risk of metabolic syndrome, or diabetes incidence.

First, in a cross-sectional analysis of data from the Woman on the Move through Activity and Nutrition (WOMAN) study [43], Casas et al. [44] examined the independent and combined associations between self-reported LTPA, sleep quality and duration (from the Pittsburgh Sleep Quality Index [PSQI]), and several measured CVD risk factors in 393 postmenopausal

overweight or obese women. Each behavior (LTPA, sleep quality, and sleep duration) was independently associated with at least one CVD risk factor in the expected direction after controlling for the other behaviors and known confounders (e.g., age, smoking etc.). In combined associations, women with higher LTPA (above median split) had better body composition and more favorable metabolic profiles compared to women with low LTPA (below median split), after controlling for sleep quality and duration. However, there were no association between sleep quality or duration and CVD risk factors in women of the same PA level. Nonetheless, several CVD risk factors (BMI, WC, trunk fat, total body fat, insulin, and HDL) went from most to least favorable across the following four categories: high PA/good sleep quality (PSQI score ≤ 5), high PA/poor sleep quality (PSQI score > 5), low PA/good sleep quality, low PA/poor sleep quality, suggesting an interactive effect of PA and poor sleep quality on CVD risk.

In another cross-sectional analysis of three cohorts (total N = 367) of adolescents, most with elevated blood pressure (72 %) and from a racial/ethnic minority (77 %), Countryman et al. [45] examined the interrelation between PA, aerobic fitness, and sleep with the metabolic syndrome and inflammation. Using structural modeling, direct associations of self-reported PA, measured aerobic fitness (peak oxygen consumption [VO_{2peak}]), and self-reported sleep (duration, quality, and fatigue) with the metabolic syndrome and inflammation were tested. In addition, indirect associations, via fitness, of PA and sleep with the same outcomes were investigated. Their results suggested that reduced sleep duration, poor sleep quality and fatigue, and decreased PA were associated with decreased fitness, which was directly related to an increased risk of metabolic syndrome and inflammation in these at-risk youth. The concept that PA and sleep would be indirectly linked with metabolic profile through physical fitness is original and thought provoking. However, these findings, as well as those from Casas et al. [44], should be taken with consideration of the fact that they were derived from relatively small samples of specific at-risk populations (postmenopausal women and adolescents predominantly hypertensive and from a racial/ethnic minority). They were conducted using adequate measurement tools, but can nevertheless not be generalized to common adult populations.

A handful of studies (three cross-sectional and one secondary analysis of a lifestyle intervention trial) have been conducted in representative adult samples from Portugal [42], Finland [46], and the United States [47, 48]. In Santos et al.'s [42] cross-sectional study, the

association of 12-month recalls of PA, sleep duration, and other behaviors with the metabolic syndrome was examined in 2 164 Portuguese adults. After adjusting for confounders and other behaviors, greater total PA (males and females), work activities (females only), household activities (males only), and short (≤ 6 hours/day) sleep duration (females only) were associated with a lower risk for the metabolic syndrome. Longer sleeping hours (males and females) were independently associated with a higher risk of having the syndrome. The finding regarding a potential protective role of short sleep time contrasts with many prior reports, which have observed a U-shaped association between sleep duration and risk for obesity, metabolic syndrome, and type 2 diabetes [46] [49, 50]. However, this association was observed in female participants only. Furthermore, sleep duration and PA were based on a long (12-month) recall time, and sleep duration was assessed with a single interview question.

In a secondary analysis of data from the Finnish Diabetes Prevention Study [51], a randomized controlled lifestyle intervention trial, Tuomilehto et al. [46] examined the association between sleep duration and type 2 diabetes in 522 overweight adults with impaired glucose tolerance. Participants in the larger trial were randomly allocated either to a group receiving an intensive individualized diet-PA counseling or to a control group. The median duration of the intervention and post-intervention periods were, respectively, four years and three years, for a total follow-up of seven years. Sleep duration was assessed at baseline and annually through 24-hour activity recall and grouped as ≤ 6.5 hours, 7-8.5 hours, 9-9.5 hours, and ≥ 10 hours. Self-reported LTPA and other potential confounders were also measured at baseline and annually. Changes in sleeping hours during the follow-up period were minor, such that no significant shifting in sleep duration group occurred in either group. During the three-year post-intervention follow up, about a third of participants (n = 182) developed diabetes. A trend for an increased risk for type 2 diabetes was seen in short sleepers (≤ 6.5 hours). Long sleep duration was significantly associated with increased diabetes risk in the control group, but not in the group receiving intensive individualized diet-PA counseling. This interaction between intervention group and sleep duration on diabetes incidence appeared to be independent of morphometric, metabolic, and inflammatory parameters, since these were similar across sleep duration groups at baseline and changed to a similar degree in both intervention arms. These findings suggest a potential protective role of intervention-induced increases in PA (or possibly fitness) in the risk of developing diabetes for overweight adults with impaired glucose tolerance

and long sleeping durations. However, long sleepers in this trial were more likely to be on antihypertensive medication compared to other participants. This may have introduced a bias, since this type of medication has been associated with tiredness, fatigue, and sleep disorders [52].

An important concept considered, but not accounted for, in these previous studies is the interdependent association between sleep, PA, and SB. In fact, the amount of time allocated to sleep, PA, and SB is inter-dependent: increasing time in one of these behaviors requires decreasing time in another, which may in turn affect CVD risk. In line with this concept, Buman et al. [47] used isotemporal substitution modeling to examine whether a decrease in one behavior in favor of another would be associated with objective changes in various CVD risk factors in a large cross-sectional analysis (N = 2 185) of data from the United States' National Health and Nutrition Examination Survey (NHANES). Sleep duration was measured with a single interview question, while SB and PA (light and moderate/vigorous) were objectively measured with accelerometry. After holding all other time constant and adjusting for potential confounders, associations with a more favorable CVD risk profile were observed from reallocating time from SB to any other behavior, including sleep. However, moderate/vigorous PA appeared to be the most potent health-enhancing behavior, with 2-25 % improvements in waist circumference, lipid metabolism, and glucose metabolism seen from reallocating 30 minutes/day from SB (and, to a lesser extent, from sleep and light PA) to additional moderate/vigorous activity. In general, the observed benefits of reduced time in SB and more time in active behaviors were similar across sleep duration categories. In the limited cases where there was an interaction with sleep, less time in SB and more in active behaviors were typically protective or synergetic in very short sleepers (≤ 5 hours). Once again however, given the methodology used to assess sleep, no information was available on actual sleep duration (versus time in bed), sleep quality (objective or subjective in this case), or presence of a sleep disorder.

Recently, in another cross-sectional analysis of NHANES data, Saleh and Janssen [48] investigated the associations between accelerometry-derived sleep duration (divided into quartiles) and SB (quartiles of sedentary time and tertiles of screen time) with the occurrence of the metabolic syndrome in 1 371 adults. Their main findings were that SB was very weakly and insignificantly correlated with sleep duration. After adjusting for confounders, including

accelerometry-determined moderate/vigorous PA, sleep duration was not significantly associated to the metabolic syndrome or its components, while SB was, independent of sleep duration. Although sleep was objectively measured in this study, it was done so through a proxy estimate (longest non-wear period in a 24-hour cycle, with at least two valid measurement days). Accordingly, no details on the presence of a sleep disorder were available.

Together, these studies suggest that higher PA levels are consistently associated with improved CVD risk profiles even after adjusting for sleep. The impact of shorter or longer sleeping durations (compared to the average 7-8 hours/day) on CVD risk profile may vary according to levels of PA and/or SB. Increasing PA levels and/or reducing SB may have a protective effect in very short and very long sleepers, but this will have to be confirmed. Most studies conducted to date have been cross-sectional and have used subjective measures of sleep and PA. Future research with longitudinal or experimental designs and objective assessments of sleep (duration and quality) and PA is needed. In addition, the impact of experimentally reallocating time from SB to sleep and/or PA should be investigated.

Sleep, Physical Activity, and Cardiovascular Events

Several population-based epidemiological studies have evaluated the impact of subjective measures of PA and sleep on the incidence of fatal [53-55] and non-fatal [53, 55] cardiovascular (CVD) events. In a longitudinal study of 6 672 men and 7 769 women from the Netherlands, sufficient physical activity, defined as at least 3.5 hours of cycling or sports per week, and sufficient sleep, defined as a sleep duration of at least 7 hours, were both independently associated with lower incidence of fatal and non-fatal CVD events over the follow-up period lasting an average of 12 years [53]. Furthermore, adoption of a greater number of healthy lifestyle behaviors, including PA, sleep, smoking status, alcohol consumption, and a Mediterranean diet, was associated with greater decreases in risk for CVD events, highlighting the cumulative impact of these different lifestyle behaviors.

Similar findings were observed in a sample of 44 056 participants from the Singapore Chinese Health Study [55]. Cardiovascular mortality was higher among individuals with sleep durations of less than 6 hours or more than 9 hours per night and among individuals with less than 2 hours of moderate strenuous activity per week. Importantly, the accumulation of

protective lifestyle factors, including sleep, PA, smoking, alcohol intake, dietary, and BMI, was associated with a linear decrease in coronary heart disease, cerebrovascular disease and overall cardiovascular mortality. This effect was observed for both healthy individuals and individuals with a history of CVD or diabetes mellitus at enrollment.

In a 16.5-year longitudinal of 44 301 Japanese individuals, the adoption of multiple healthy lifestyle behavior was associated with lower cardiovascular mortality [56]. In this study, walking ≥ 1 hour/day, participating in sport ≥ 5hour/week, and sleeping 5.5-7.4 hour/night were considered protective. When considering individuals with the lowest (0-2) healthy lifestyle scores compared to those with the highest (7-8) scores, mortality rate from stroke, coronary heart disease, and other CVD decreased to $1/3^{rd}$ for men and $1/4^{th}$ for women.

In a 15-year follow up of 70 973 Swedish participants, Bellavia et al. [54] specifically investigated the relationship between sleep duration and CVD-related mortality across categories of PA. Results indicated that cardiovascular mortality was higher among participants with a sleep duration of less than 6 hours or more than 8 hours per night, than for participants with a sleep duration of 7 hours. However, this effect was modulated by PA. Although short sleep duration was associated with higher mortality at all PA levels, the effect was more pronounced among individuals in the lower PA tertile. Furthermore, long sleep duration (> 8 hours) was associated with greater mortality only for individuals in the lower PA tertile. This is in line with the suggestions that low levels of PA influence the association between long sleep duration and mortality rate [57].

Collectively, results from these epidemiological studies indicate that adopting a greater number of healthy lifestyle behaviors decrease CVD risk [55-58], that sufficient sleep makes a unique contribution to this reduction [55], and that sleep and physical activity interact to predict CVD risk, such as the impact of short and long sleep duration on CVD mortality is greater among individuals with lower PA level [56].

Bidirectional relationship between PA and Sleep

In addition to the interactive effect of PA and sleep on CVD risks, there seems to be a reciprocal relationship between these two lifestyle factors. Epidemiological studies indicate that

greater involvement in PA is associated with overall better sleep quality [58]. Randomized exercise intervention studies corroborate that involvement in regular PA, particularly aerobic exercise, is associated with an improvement in both subjective and objective sleep quality [59, 60], although this effect appears to be more pronounced among individuals with poor sleep [61]. A few recent studies have specifically examined the reciprocal relationship between PA and sleep. In a 2-year longitudinal study with healthy older adults, cross-lagged analysis indicated that sleep quality at baseline predicted PA at the 2-year follow-up [62], while baseline PA did not predict subsequent sleep quality. Furthermore, in a daily diary study in women with insomnia, poor sleep on a given night was associated with shorter exercise duration the following day, but exercise duration on a given day did not predict sleep quality on the corresponding night [63]. A similar pattern of results was observed among older adults without sleep complaints. Participants reported more PA following nights when their sleep quality was rated as above their personal mean sleep quality level and they reported better sleep quality following days when their PA levels was above their personal mean PA level [64] Taken together, these results suggest that involvement in regular physical activity is associated with an overall improvement in sleep quality. However, poor sleep on a given night can impact involvement in PA the following day. Individuals with sleep complaints may be particularly sensitive to the effect of poor sleep on next-day involvement in PA. These data highlights the importance of considering poor sleep as an obstacle to the maintenance of regular PA.

Limitations and future directions

The majority of studies published to date have used subjective measurements, such as self-administered questionnaires, to evaluate sleep and PA. Moreover, the specific subjective tools used and the grouping values for each behavior have differed from one study to the other. This could explain some of variability in the findings. Further research with more objective measurements, especially for sleep, is needed to overcome this limitation. Likewise, most studies have been cross-sectional and observational in nature and other confounding factors, such as age, gender, and socio-economic status, have not always been taken in consideration. Therefore, more longitudinal follow up studies are needed to clarify the independent, combined, and interactive role of these two health behaviors on CVD risk.

Conclusion

In summary, adequate sleep and higher PA are both necessary to maintain a healthy lifestyle and prevent risk to develop CVD. Furthermore, sleep and PA are lifestyle behaviors that can interact to influence CVD risk. Overall, maintaining optimal sleep duration and sleep quality, reducing sedentary time and increasing PA, especially moderate to vigorous PA, seems to be the best method to manage risk of metabolic syndrome and subsequent CVD. In addition, fatal or non-fatal cardiovascular events can be prevented or postponed by obtaining adequate average sleep duration (7-8 hours/day) and greater levels of PA in combination with other protective lifestyle factors, such as well balanced dietary pattern, light-moderate alcohol consumption, non-smoking, and maintenance of a healthy body weight. More intervention studies simultaneously targeting sleep, physical activity, and sedentary behavior are needed.

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Table 1. Methodological Overview of Studies on the Interactive Effect of Sleep and PA on Cardiovascular Risk Profile

Reference	Design	Study Population N (M:F)	Descriptives	Independent Variables Sleep	Activity	Dependent Variables
Di Milia et al., 2013 [29]	Cross-sectional	N=1 162 (450:622)	Random sample of Australian adults Age=45.2 ± 11.2 yrs	Sleep duration (self-report questionnaire)	PA intensity (IPAQ) and sitting duration (WSQ)(both self-reported questionnaires)	BMI (from self-reported values)
Vioque et al., 2000 [30]	Cross-sectional	N=1 772 (814:958)	Random sample of Spanish adults Age >15 yrs	Sleep duration (self-reported questionnaire)	SB/LTPA (self-reported questionnaire)	BMI (objectively measured)
Forgelholm et al., 2007 [31]	Cross-sectional	N = 7 641 (3 377:4 264)	Random sample of Finnish adults Age=54.6±16.3 yrs	Sleep duration SRD (interview questionnaire)	LTPA (questionnaire)	WC and BMI (objectively measured)
Laurson et al., 2014 [32]	Cross-sectional	N = 9 589 (4 715:4 874)	U.S. high-school students (grades 9-12)	Sleep duration (self-report questionnaire)	PA (self-report questionnaire)	BMI (from self-reported values)
Garaulet et al, 2011 [33]	Cross-sectional	N = 3 311 (1 563:1 748)	European adolescents Age=12.5–17.5 yrs	Sleep duration (interview question)	PA (accelerometry and IPAQ-A)	Morphometry (BMI, WC, hip circumference, body fat, fat mass index)
Chaput et al., 2009 [34]	Longitudinal (6-year follow-up)	N = 283 (121:162)	Sample of French Canadian adults from white two-parent families, more than half of which included at least one parent or offspring with BMI ≥ 32 kg/m^2 Age=18-64 yrs (baseline)	Sleep duration (self-report questionnaire)	PA (self-reported 3-day activity diary)	Weight and BMI (objectively measured)
Patel et al., 2006 [35]	Longitudinal (16-year follow-up)	N = 68 183 (0:68 183)	Sample of female, married registered nurses, free of comorbid disease Age=39-65 yrs (baseline)	Sleep duration (self-report questionnaire)	PA (self-report questionnaire)	Weight and BMI (from self-reported values)
Casas et al., 2012 [44]	Cross-sectional	N = 393 (0:393)	Postmenopausal overweight/obese women Age=62±3 yrs	Sleep quality and duration (self-report questionnaire: PSQI)	LTPA (MAQ)	Morphometry (BMI, WC), body composition (DXA), BP, blood profile (total cholesterol, triglycerides, HDL-C, insulin, glucose)
Countryman et al., 2013 [45]	Cross-sectional	N = 367 (268:99)	U.S. adolescents Age=16±0.7 yrs	Sleep duration (7-day interviewer-administered AR), sleep quality and fatigue (items 16-17 from the CDI)	PA (7-day interviewer-administered AR), aerobic fitness (measured VO_{2peak})	Occurrence of metabolic syndrome (defined based on Shen et al.'s model [65]) and inflammation (elevated fibrinogen, high-sensitivity CRP, IL-6)

Santos et al., 2007 [42]	Cross-sectional	N=2 164 (832:1 332)	Random sample of Portuguese adults Age =18-92 yrs	Sleep duration (single interview question, 12-month recall)	Total PA, work activities, household activities, LTPA (all in MET/hour), regular exercise (yes/no) (interview questionnaire, 12-month recall)	Occurrence of metabolic syndrome (defined according to NCEP-ATPIII [38])
Tuomilehto et al., 2009 [46]	Secondary analysis from a randomized intervention trial	N= 522 (186:336)	Overweight Finnish adults with impaired glucose tolerance Age= 45-64 yrs	Baseline and annual sleep duration (24-hour self-administered AR)	LTPA Questionnaire	Incidence of diabetes (defined as per WHO 1985 criteria [66]) per 100 person-years
Buman et al., 2013 [47]	Cross-sectional	Full sample: N=2 185 (1 157:1 028) Fasting sub-sample: N=923 (431:492)	Random sample of the U.S. civilian non-institutionalized population Age ≥ 20 yrs	Sleep duration (single interview question with 5 levels: ≤ 5 hours, 6 hours, 7 hours, 8 hours, or ≥ 9 hours)	SB (<100 counts/min), LIPA (100-1951 counts/min), MVPA (≥ 1952 counts/min) (7-day accelerometry)	Morphometry (WC), BP, blood profile (nonfasting HDL, CRP; fasting LDL, triglycerides, glucose, insulin)
Saleh and Janssen, 2014 [48]	Cross-sectional	N=1 371 (770:601)	Random sample of the U.S. civilian non-institutionalized population Age ≥ 20 yrs	Sleep duration (accelerometry-derived proxy estimate from longest non-wear period in 24-hour cycle on ≥ 2 valid days)	SB, divided into screen time (2 interview questions) and sedentary time (time spent below 100 counts/min with 7-day accelerometry)	Occurrence of metabolic syndrome (defined according to criteria from a WHO Expert Consultation [39])

AR: Activity Recall, BMI: Body Mass Index, BP: Blood Pressure, CDI: Children's Depression Inventory, CRP: C-Reactive Protein, DXA: Dual-Energy X-Ray Absorptiometry, F: Females, HDL-C: High-Density Lipoprotein Cholesterol, IL-6: Interleukin-6, IPAQ: International Physical Activity Questionnaire, IPAQ-A: International Physical Activity Questionnaire for Adolescents, LIPA: Light-Intensity Physical Activity, LTPA: Leisure-Time Physical Activity, M: Males, MVPA: Moderate-to-Vigorous Physical Activity, MAQ: Modifiable Activity Questionnaire, MET: Metabolic Equivalent of Task, NCEP-ATPIII: National Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), PA: Physical Activity, PSQI: Pittsburgh Sleep Quality Index, SB: Sedentary Behavior, SRD: Sleep-Related Disturbances, VO_{2peak}: Peak Oxygen Consumption, WHO: World Health Organization, WC: Waist Circumference, WSQ: Workforce Sitting Questionnaire.

Table 2. Methodological Overview of Studies on the Interactive Effect of Sleep and PA on Cardiovascular Events

Reference	Design	Study Population N (M:F)	Descriptives	Independent Variables Sleep	Activity	Dependent Variables
Hoevenaar-Blom et al., 2013 [53]	Retrospective analysis, Between 1994-1997, End of follow-up 2008	N=14 639 (6 672:7 967)	Europeans (Dutch) Age=20–65 yrs (41±11)	Sleep duration (self-administered questionnaire) <7 vs ≥ 7hrs/night	Cycling and sport (self-administered questionnaire) _<3.5 vs. ≥3.5 hrs/wk cycling and sports	CV events (nonfatal or fatal MI, stroke)
Odegaard et al., 2011 [55]	Retrospective analysis, From 1993-1998, End of follow-up 2009	N=50 466	Chinese Age=45-74 yrs, (44 056 without a history of DM, CVD, or cancer and 6 410 with DM or history of clinical CVD)	Sleep duration (interview questionnaire) 6-8 vs. <6 or ≥ 9 hrs/night	MVPA (interview questionnaire) <2 vs. ≥2 hrs/wk of moderate or any strenuous activity	CV events (mortality from CVD, CHD, stroke)
Eguchi et al., 2012 [56]	Retrospective analysis, Between 1988-1990, End of follow-up 2006	N=43 010 (18 747:24 263)	Japanese Age =40-79 yrs (men: 55.6 yrs, women: 56.1 yrs)	Sleep duration (self-administered questionnaire) 5.5–7.4 vs. <5.5. and ≥ 7.5 hrs/night	Walking <.5h/day or exercise < 5h/week vs ≥ .5hr/days or exercise ≥ 5hr/week (self-administered questionnaire)	CV events (mortality from CVD, CHD, and stroke)
Bellavia et al., 2014 [54]	Retrospective analysis, 15-yr follow-up between 1998-2012	N=70 973 (37 846:33 127)	Swedish Age= 45–83 yrs	Sleep duration (self-administered questionnaire) 6.6–7.4 hrs/night	Activity levels during different activities 1st tertile = <39.3 MET hrs/day 2nd tertile = 39.3–44.2 MET hours/day 3rd tertile = >44.2 MET hours/day	CV events (mortality form CVD and stroke)

CHD: Coronary Heart Disease, CV: Cardiovascular, CVD: Cardiovascular Disease, DM: Diabetes Mellitus, F: Females, M: Males, MVPA: Moderate-to-Vigorous Physical Activity, MET: Metabolic Equivalent of Task, MI: Myocardial Infarction.