Clinical Implications of Diurnal Variations in Physiological, Psychological and Behavioral Measures in Patients with Chronic Obstructive Pulmonary Disease

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ABSTRACT

Clinical Implications of Diurnal Variations in Physiological, Psychological and Behavioral Measures in Patients with Chronic Obstructive Pulmonary Disease

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The aim of this thesis was to investigate the clinical implications of diurnal variations in physiological, behavioral and psychological measures in a Chronic Obstructive Pulmonary Disease (COPD) population. In a sample of 14 moderate-to-severe COPD participants we first evaluated the effect of time of day on the acute response to incremental exercise in COPD. We found that a majority of individuals exceeded clinically significant changes in their pulmonary function and peak exercise capacity measures. A peak in exercise capacity was observed in the afternoon in the subgroup of individuals who demonstrated increased variability, similar to the timing of peak exercise performance previously documented in healthy individuals. We then investigated if high or low relative amplitude (RA), a marker of internal synchronization, was associated with disease severity or prognosis in COPD. Lower RA was associated with higher ratings of dyspnea and worse scores on prognostic indexes. The amplitude difference between the two sub-groups appears to be due to increased physical activity at midday in the high-RA sub-group. Lastly, we investigated whether diurnal variation in depression symptoms would be associated with depression symptoms severity. We found larger diurnal variation in depression symptoms to be associated with worse depression symptom severity in COPD patients. This association seemed independent of pulmonary function and exercise capacity.

The results presented in this thesis were the first to report on diurnal variations in various common clinical measures in COPD and to explore the link between amplitude of the rest-activity cycle and indexes of disease prognosis. Based on our findings, accounting for the timing of repeated exercise testing is suggested. RA of the rest-activity cycle may be a useful marker in COPD prognosis. Lastly, identifying diurnal variation in depressive symptoms may help detect depression in COPD.

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CONTRIBUTION OF AUTHORS

The content of this thesis is based on three articles, all of which have been published. It should be noted that the three articles result from one comprehensive protocol, which was written at the beginning of the project. In keeping with the Concordia University Thesis Regulations, a uniform referencing style, a single comprehensive reference list is given at the end of the thesis, and the consecutive numbering of the tables and figures is used. Below are the details for each of the authors' contribution to the articles.

Clinical Impact of Time of Day on Acute Exercise Response in COPD

This original research paper was published in the Journal of Chronic Obstructive Disease in 2014. I was the primary author and responsible for the original idea, which was based on my clinical experience with exercise evaluations and the clinical population. I conducted the literature review and collaborated on the comprehensive protocol design, wrote ethics consent form, recruited and collected data, created databases from the measures from the exercise tests and pulmonary function evaluations, performed data analyses and interpretation of the results, and wrote the manuscript. Drs. Dumont and Pepin were instrumental in the conception of the protocol design, obtaining ethics approval, interpreting the results, ensuring the accurateness and completeness of the article, and providing critical revision of the article. Dr. Moullec collaborated on the protocol design, aided in the statistical analyses, and provided critical revision of the article. Dr. Rizk and Ms. Wardini (M.Sc.) assisted in the recruitment of participants and setup of evaluations and reviewed the article for publication. Ms. Trutchnigg (M.Sc.) assisted with the data collection and reviewed the article for publication. Ms. De Lorimier (PT) assisted with the recruitment of the participants and reviewed the article for publication. Dr. Parenteau provided medical supervision of the evaluations and reviewed the article for publication. The re-print of the article, along with the copyright permission form, can be found at the end of the thesis in Appendix B.

Amplitude of Rest-Activity Rhythms in Chronic Obstructive Pulmonary Disease

This article had been accepted for publication to the ChronoPhysiology and Therapy Journal in September 2016. I was the primary author and responsible for the conception of the idea for the project, which built upon previous research findings, I conducted the literature review, collected follow up data from medical dossiers, created the circadian rest-activity and sleep databases from actigraphy and diary data, performed data analyses, interpreted the results, and wrote the manuscript. Drs. Dumont and Pepin were instrumental in the conception of the project, interpretation of the results, and ensured the accurateness and completeness of the article and provided critical revision of the article. Dr. Moullec provided critical revision of the article. Ms. Parwanta (M.Sc.) and Trutschnigg (M.Sc.) assisted in the collection of the data and revised the article for publication. Dr. Paquet aided in the statistical analyses and figures, and revised the article for publication.

Diurnal Variations in Psychological Distress in Chronic Obstructive Pulmonary Disease

This article was accepted for publication and has been published as an e-publication ahead of print in 2016 in the Journal of Rehabilitation Nursing. I was the primary author and responsible for the conception of the idea for the project, I conducted the literature review, created the database for measures of psychological distress, performed data analyses and interpreted the results, and wrote the manuscript. Drs. Moullec and Pepin were instrumental in the conception of the project, interpretation of the results, and ensured the accurateness and completeness of the article and provided critical revision of the article. Dr. Dumont provided critical revision of the article. Dr. Rizk assisted in the double data entry and revised the article for publication. Ms. Parwanta (M.Sc.) reviewed the article for publication. The copyright permission form can be found at the end of the thesis in Appendix B.

In addition to working on my graduate studies projects I have had the opportunity to work with a number of collaborators. Included in Appendix C is the publication The Role of Sleep and Physical Activity on the Risk for CVD, published in the Current Cardiovascular Risk Report in 2014, which was a topic related to my thesis along with its copyright clearance forms.
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List of Abbreviations

ACCP – American College of Chest Physicians

ADO – age, dyspnea and airflow obstruction index

ANCOVA – analysis of covariance

ANOVA – analysis of variance

ATS – American Thoracic Society

BMI – body mass index

BODE – body composition, airflow obstruction, dyspnea, exercise capacity index

BODEx – body composition, airflow obstruction, dyspnea, exacerbations index

CAT – COPD assessment test

CES-D – Center for Epidemiological Studies Depression Scale

COPD – chronic obstructive pulmonary disease

COTE – COPD specific comorbidity test

CPET – cardiopulmonary exercise test

CTS – Canadian Thoracic Society

DSM-V – Diagnostic and Statistical Manual of Mental Disorders, 5^{th} edition

EMA – ecological momentary assessment

ERS – European Respiratory Society

ERV – expiratory reserve volume

FEV_1 – forced expiratory volume in one second

FRC – functional residual capacity

FVC – forced vital capacity

GOLD – Global initiative for chronic obstructive pulmonary disease

HR – heart rate

IC – inspiratory capacity

IRV – inspiratory reserve volume

mBODE% - modified BODE index, with percent VO_2

MCID – minimal clinical important difference

MEQ – Morning and Eveningness Questionnaire

mMRC – modified medical research council dyspnea scale

QID – quarter en die or four times a day

RA – relative amplitude

RER – respiratory exchange ratio

RR – respiratory rate

RV – residual volume

SpO_2 – pulse oximetry or oxygen saturation

TLC – total lung capacity

TST – total sleep time

VC – vital capacity

VCO_2 – carbon dioxide production

VE – minute ventilation

VO_2 – oxygen consumption

VS-CES-D – very short CES-D

V_T – tidal volume

WASO – wake after sleep onset

Wpeak – peak exercise capacity

1.0 THEORETICAL CONTEXT

1.1 Burden of COPD

Chronic Obstructive Pulmonary Disease (COPD) has been defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as "*a common, preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airway and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients" [1]*.

The Canadian Thoracic Society (CTS) generally agrees with the GOLD definition, *COPD "is a respiratory disease largely caused by smoking, and is characterized by progressive, partially reversible airway obstruction and lung hyperinflation, systemic manifestations and increasing frequency and severity of exacerbations"* [2].

Combining these definitions will help explain what is COPD. The definition by CTS specifies the cause of COPD being mainly due to cigarette smoking. In time the majority of smokers develop a certain amount of airflow limitation, however, not all smokers end up developing COPD [3]. Factors such as the age an individual starts smoking, the number of pack years (the product of smoking duration and number of cigarettes smoked per day), and current smoking status are all contributing determinants in the development, progression and outcome of COPD [2, 4, 5]. Individuals over the age of 45 years are more at risk of developing COPD as it results from cumulative exposures to noxious particles or gases (including environmental or workplace exposures) compounded by time [1]. As stated by the GOLD guidelines, an abnormal inflammatory response is invoked by the inhalation of noxious particles [1]. Once COPD becomes established, the inflammatory response persists even in the absence of continued exposure from noxious particles [6]. The enhanced chronic inflammatory response leads to changes in the normal defense mechanism. Excessive mucous secretion, airway remodeling, and tissue destruction obstruct airflow, especially during expiration [1]. Air can become trapped within the lungs from a weakened structure or if inhalation is instigated before full exhalation is reached [7]. The trapped air within the lungs causes lung hyperinflation. It's hypothesized that most individuals with COPD have some lung hyperinflation [7]. Hyperinflation may occur with increased disease severity or during exacerbation as a function of increased respiratory rate and expiratory flow limitation [7]. An exacerbation may be triggered by a lung infection and is the sudden worsening of respiratory symptoms of dyspnea, cough or sputum production exceeding day-to-day variations [1, 8,

9]. The systemic manifestations of the disease, such as muscle wasting and systemic inflammation, may lead to other comorbid disease conditions, increased hospitalizations and mortality [10]. In general, a COPD diagnosis is considered treatable [1]. Symptoms, associated comorbidities, and quality of life can be improved with good disease management.

In Canada and around the world, COPD is recognized as the fourth ranked cause of death [1, 2]. Approximately 210 million people around the world have COPD [11], and 2.6 million (17%) of Canadians have airflow obstruction compatible with stage I, or mild COPD disease severity [12, 13]. Previous estimates, based on self-reported surveys reported a prevalence of around 700 000 (4%) within the Canadian population [2], which has long been thought to be an underestimation of the actual prevalence of the disease in Canada and in other countries [2, 12, 13]. The incidence of COPD is approximately three per 1000 person years in individuals older than 40 years [14, 15]. The incidence rate increases with age; between the ages of 60 to 89 years the incidence rate is around seven per 1000 person years [15]. The incidence rate is also greater in men than women [14, 15].

COPD is a leading cause of increased morbidity in Canada [2]. Morbidity from COPD is measured from documented hospitalizations and physician visits, and may be due to exacerbations and other comorbid conditions related to COPD (ie. cardiovascular disease, diabetes, etc.) [1]. The economic burden resulting from COPD is significant. In general, costs increase with worsening of the disease severity and the greatest proportion of the economic cost has been associated with the occurrence of exacerbations [1]. In Canada, it has been estimated that direct costs incurred per year is approximately $2,000 per patient [16]. Additionally, indirect costs are incurred from the loss of work productivity, cost of home caregivers, etc. Therefore, Canadians with COPD may be associated with an economic burden of slightly over $3,000 per patient per year [16]. In 2011, societal cost of COPD was an estimated $4.52 billion in Canada [17]. That's billions of dollars to treat and manage COPD every year in Canada.

1.2 Assessment of Factors Affecting COPD

1.2.1 Describing lung volume and capacities

To better understand lung function and measures of airflow limitation, a brief overview of the lung volumes and capacities are described here, and illustrated in Figure 1.

There are four lung volumes. The tidal volume (V_T) is the volume of air we inspire and expire within a respiratory cycle [18]. Should we need to take a larger inspiration, we can tap into our inspiratory reserve volume (IRV), which is the maximal volume of air we can inspire beyond the usual resting V_T [18]. Similarly, the expiratory reserve volume (ERV) is the volume of air we can expire

maximally beyond the usual resting V_T [18]. However, even when we maximally expire there is a volume of air, which remains trapped in the lungs and this is the residual volume (RV) [7, 18].

There are four lung capacities, which can be directly measured or calculated from the sum of at least two lung volumes. The inspiratory capacity (IC) is the maximal volume of inspired air and is the sum of the V_T and IRV. The functional residual volume (FRC) is the maximal reserve volume of air and is the sum of ERV and RV. The vital capacity (VC) is the maximal volume of air which can be inspired and expired voluntarily and can be calculated from the sum of the IRV, VT and ERV, or from summing the IC and ERV. Finally, the total lung capacity (TLC) is the total volume of the lungs and is the sum of all four volumes.

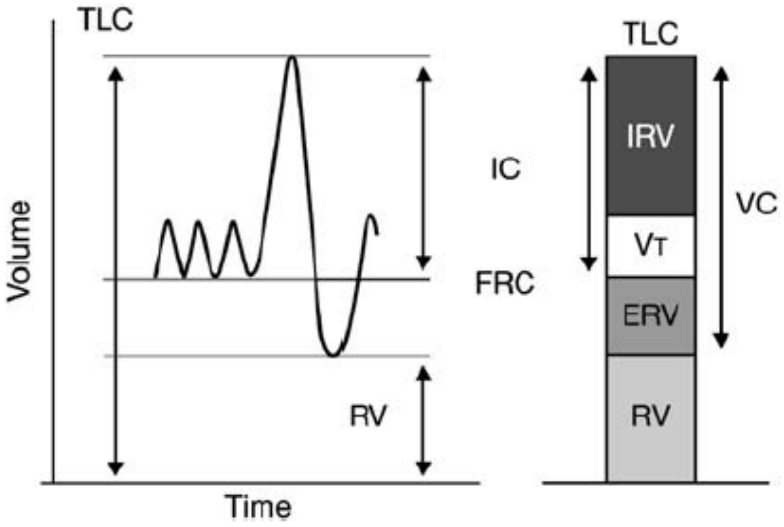

Figure 1 - Lung volumes and capacities [7]. Lung volumes include; tidal volume (V_T), inspiratory reserve volume (IRV), expiratory reserve volume (ERV) and residual volume (RV). Lung capacities include; inspiratory capacity (IC = IRV + V_T), functional residual capacity (FRC = ERV + RV), vital capacity (VC = IRV + V_T + ERV or IC + ERV) and total lung capacity (TLC = IRV + V_T + ERV + RV).

1.2.2 Spirometry

The current standards from the American Thoracic Society (ATS), the European Respiratory Society (ERS) [9], as well as GOLD [1] recommend that the diagnosis of COPD be considered if an individual presents with symptoms such as chronic cough, dyspnea, and sputum production, or has a history of smoking or long-standing occupational exposure to biomass fuels, occupational dust or chemicals. The CTS [2] recommendation suggests using the following as a screening protocol;

"*patients who are older than 40 years of age and who are current or ex-smokers should undertake spirometry if they answer yes to any one of the following questions; 1) Do you cough regularly?, 2) Do you cough up phlegm regularly?, 3) Do even simple chores make you short of breath?, 4) Do you wheeze when you exert yourself, or at night?, 5) Do you get frequent colds that persists longer than other people you know?"* A COPD diagnosis is confirmed when spirometric measures identify airflow obstruction.

Spirometry is a test, which measures the flow or volume of inspired and expired air within a specified amount of time [18, 19]. The assessment of the forced vital capacity (FVC), the forced expiratory volume in one second (FEV_1) and the FEV_1/FVC are essential for diagnosis of COPD. The FVC is the amount of volume measured from maximal inspiration to complete and forceful expiration. The FEV_1 is assessed within the first second of forceful expiration and determines the extent of airflow limitation. Values are obtained in liters as well as percent of predicted, which accounts for differences in age, sex, height and ethnicity [18]. The ratio of FEV_1/FVC is calculated to standardize for each individual's FVC.

In order to diagnose COPD, spirometry should be performed after receiving a dose of short-acting inhaled bronchodilator [1]. The GOLD criterion to confirm the presence of airflow limitation depends upon a post-bronchodilation fixed ratio of $FEV_1/FVC < 0.70$ [20]. COPD can be further classified into GOLDs grading system; GOLD 1 or mild COPD has an $FEV_1 \geq 80\%$ predicted, GOLD 2 or moderate COPD with $50\% \leq FEV_1 < 80\%$ predicted, GOLD 3 or severe COPD with $30\% \leq FEV_1 < 50\%$ predicted and GOLD 4 very severe COPD with $FEV_1 < 30\%$ predicted [20]. The measure of FEV_1 by itself has a weak correlation with clinical outcomes like quality of life and symptoms [1]. In 2011, GOLD changed their classification scheme to recommend a combined assessment, which includes spirometric assessments (GOLD grading system 1, 2, 3 or 4), symptoms (COPD assessment test (CAT) [21] or modified Medical Research Council dyspnea scale (mMRC) [22]), and number of exacerbations in the previous year (Figure 2). The use of this composite measure was aimed at improving the ability of predicting prognosis and outcome.

The CAT is a short comprehensive questionnaire, which assesses symptoms such as cough, sputum, chest tightness, breathlessness, activity, confidence, sleep and energy [21]. CAT it is an 8-item questionnaire, with a score ranging from 0 to 40; a larger value corresponds to more severe symptoms [21]. In the absence of the CAT, then the mMRC dyspnea scale may be used. The mMRC is a 5-item questionnaire, with a score ranging from 0 to 4; a larger value corresponding with greater amounts of breathlessness [22].

The risk of exacerbation is based on the number of exacerbations that occur per year. More than

two exacerbations per year is considered higher risk and may affect the management of COPD [9].

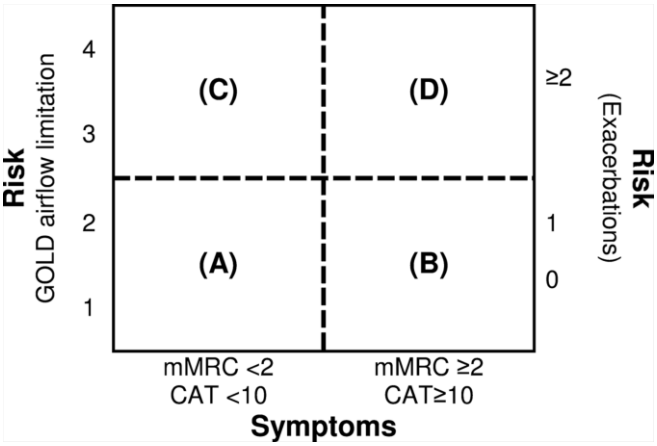

Figure 2 – Combined COPD assessment [1]. Four groups result with Group A being low risk and less symptoms, Group B is low risk and more symptoms, Group C is high risk and less symptoms and Group D is high risk and more symptoms.

1.2.3 Symptoms

Symptoms have received greater significance in this new combined COPD assessment. Respiratory symptoms play an important role; chronic cough, dyspnea, sputum production, wheezing or chest tightness are what often lead a person to seek medical attention [1]. In certain cases symptoms may precede airflow limitation or alternatively airflow limitation may develop without symptoms [1]. The presentation of symptoms is variable from day-to-day and from person-to-person [1]. Additional symptoms, which have been investigated, are fatigue, sleep disturbance, symptoms of anxiety and depression, cognitive impairment (poor memory), etc. [1]. In a study by Kinsman et al. [23], they categorized the most frequently reported symptoms in COPD and in order of most to least reported are symptoms of dyspnea, fatigue, sleep disturbance, congestion, irritability, symptoms of anxiety and depression (decathexis/withdrawal, helplessness/hopelessness), poor memory, peripheral complaints and alienation. These collateral symptoms, along with the classic symptoms, may be important targets for disease management and may be important in determining disease prognosis.

1.2.4 Exercise tolerance

In COPD, multiple factors may contribute to exercise tolerance. Exercise capacity may be evaluated via a cardiopulmonary exercise test (CPET), and maximal effort is determined when a plateau in oxygen consumption (VO_2 max) is reached [24]. However, in COPD, premature termination may occur before this physiological end-point. The two most commonly cited reasons for exercise termination in COPD are dyspnea and leg fatigue [24, 25].

Pathophysiologic changes in COPD can result in hyperinflation, which elicits symptoms of dyspnea. A more objective yet indirect measure of hyperinflation is via inspiratory capacity, which is reduced as the trapped air within the lungs increases. Dynamic hyperinflation can occur during exercise when minute ventilation and respiratory rate increase, at the expense of expiratory time [7, 26].

Dynamic hyperinflation may force the termination of exercise when oxygen demand is no longer being met [27]. Strategies to relieve hyperinflation through reduced expiratory flow resistance include; lung volume reduction surgery, oxygen therapy, continuous positive airway pressure, pursed lip breathing and pharmacological intervention. These strategies can help reduce symptoms of dyspnea and can result in improved exercise tolerance [27]. Improving exercise tolerance itself, through pulmonary rehabilitation may delay the onset of ventilatory limitation over the long-term [27]. Therefore, trained individuals will be able to do more exercise before becoming limited by ventilation.

In individuals with greater sensitivity to leg fatigue, applying certain strategies like pharmacological intervention to relieve dyspnea have not had the desired result of improving exercise tolerance [25, 28, 29]. A different mechanism of limitation associated with leg fatigue may be responsible. Pathological changes in peripheral muscle have been observed, including changes in muscle composition, with a decrease in type I (slow twitch, less fatigable) and an increase in type II (fast twitch, more fatigue prone) muscle fibers. This shift would lead to a decrease in oxidative capacity of the muscle, greater fatigue and decreased endurance capacity [30-32]. Further changes include decreased muscle mass through muscle atrophy, which may also be related to physical inactivity and deconditioning observed in COPD [31, 33]. Pulmonary rehabilitation, which includes both cardiovascular and strength training, is aimed at improving peripheral muscle function, cardiovascular, metabolic, and respiratory function and thus improves exercise tolerance [34, 35]. Adjunct strategies to improve muscle function have included: nutritional supplementation, anabolic drugs and oxygen therapy [34, 36].

The limitations to exercise can vary from person-to-person. Consequences of reduced exercise tolerance are associated with greater impairment and disability, and a reduced ability to perform activities of daily living [24, 37]. The measure of exercise intolerance may also be used as a predictor of poor quality of life and survival [38].

1.2.5 Comorbidities

Cigarette smoking, and its systemic inflammatory response, may be a shared risk factor between COPD and other diseases [1, 10]. In COPD, the most commonly associated comorbidities are cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, and lung cancer [1]. A host of comorbidities may co-exist with COPD, some of which may develop independently, and contribute to worst disease severity [1]. Comorbidities may amplify disabilities and complicate the management of COPD, as no integrated clinical management guidelines currently exists [1]. Furthermore, these comorbidities may detrimentally impact the prognosis of COPD [1]. In a study

conducted by Divo et al. [39], they recorded 79 comorbidities affiliated with COPD and found that twelve of these comorbidities increased the risk of death. Divo et al. [39] developed a COPD specific COmorbidity TEst (COTE) index, which helps assess risk of mortality in COPD. The twelve comorbidities include; lung cancer, pancreatic cancer, esophageal cancer, breast cancer, pulmonary fibrosis, atrial fibrillation/flutter, congestive heart failure, coronary artery disease, gastric/duodenal ulcers, liver cirrhosis, diabetes and anxiety. Therefore, it is important to note the most prevalent comorbidities in COPD so they can be properly managed, in addition to comorbidities with the greatest risk on prognostic outcome.

1.2.6 Psychological distress

Depression and anxiety often co-exist and are especially prevalent in COPD. Estimates of prevalence may range between 5 to 80% in COPD [40, 41]. A number of factors may explain this large range, including different methods of assessments, illness severity and setting of assessments (in-patients vs. community) [41]. In meta-analysis reviews [40, 41], the average global prevalence is estimated to be about 40%. A number of tools are available to help identify depression and anxiety, but the gold standard is described in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) [42]. The criteria for depression and for anxiety are described in Table 1 and 2, respectively. Comorbidities such as depression and anxiety often go undetected and therefore are undertreated in COPD. It has been estimated that only a third of COPD patients with depression or anxiety are being treated for the concomitant disease [43]. One possible reason may be due to the overlap in symptoms common to these diseases [44]. Symptoms common to both COPD and depression include; fatigue, poor sleep, and decreased exercise capacity [41, 42, 45]. Furthermore, a bidirectional association between psychological distress and COPD may also exist [45]. Symptoms of depression and anxiety may lead to smoking, and smoking is one of the main risk factors in the development of COPD [40, 45]. Once COPD is established the future prognosis may lead to reduced quality of life and functional capacity, which may be factors which precipitate the development of symptoms of depression and anxiety [1, 10, 45]. A few studies have found worst depression and anxiety levels to be associated with increasing GOLD disease stage classification [40, 46], while others found no significant associations [47]. COPD affects more than just the lungs, therefore using a composite measure could help recognize multiple components affecting COPD. A measure, such as the BODE index [48], which combines measures of Body composition, airway Obstruction, Dyspnea, and Exercise capacity is a better outcome predictor than lung function alone. In a number of studies [46, 47, 49], depression was found to be associated with the BODE index.

Table 1 - DSM-V Criteria for Major Depressive Disorder and Episodes

- Depressed mood or a loss of interest or pleasure in daily activities for more than two weeks.
- Mood represents a change from the person's baseline.
- Impaired function: social, occupational, educational.
- Specific symptoms, at least 5 of these 9, present nearly every day:

1. Depressed mood or irritable most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).
2. Decreased interest or pleasure in most activities, most of each day
3. Significant weight change (5%) or change in appetite
4. Change in sleep: Insomnia or hypersomnia
5. Change in activity: Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Guilt/worthlessness: Feelings of worthlessness or excessive or inappropriate guilt
8. Concentration: diminished ability to think or concentrate, or more indecisiveness
9. Suicidality: Thoughts of death or suicide, or has suicide plan

Table 2 – DSM-V Criteria for General Anxiety Disorder

- Excessive anxiety and worry (apprehensive expectation), occurring more days than not, for at least 6 months, about a number of events or activities (such as work or school activities).
- The individual finds it difficult to control the worry.
- The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months);

1. Restlessness or feeling keyed up or on edge.
2. Being easily fatigued.
3. Difficulty concentrating or mind going blank.
4. Irritability.
5. Muscle tension.
6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).

It is important to understand what impact comorbid depression or anxiety has on COPD outcomes in order to effect changes to management strategies. Comorbid depression or anxiety has been found to reduce adherence to prescribed treatments or therapies such as pharmacotherapy or pulmonary rehabilitation, decrease exercise capacity and health related quality of life, increase disability, risk of exacerbations, frequency and length of hospitalizations, and mortality [40, 50-52].

1.2.7 Composite measures of outcome

Assessments using composite measures of outcome predate the changes to the 2011 GOLD classification criteria [53]. Indeed, measures of dyspnea [54] and exercise capacity [55] have already been found to be better predictors of mortality than the measure of FEV_1. In 2004, Celli et al. [48] hypothesized that a multidimensional composite measure, combining BMI, airflow obstruction, dyspnea and exercise capacity, would demonstrate the best prediction for the risk of death, and integrated these four measures into the BODE index. Other composite measures have since been suggested, such as the modified BODE (mBODE%)[56], which substitutes the 6 minute walk distance, a submaximal measure of exercise capacity, for the percentage VO_2max obtained from an objective maximal exercise test. Other variants include the BODEx [57], which substitutes exercise capacity for the assessment of exacerbations, and the ADO [58], which assesses age, dyspnea, and airflow obstruction, but excludes BMI and exercise capacity. The BODEx and ADO were developed to be a simpler index for increased applicability outside of respiratory medicine settings. The assessment of exercise capacity may not be available at all sites, and therefore alternate indexes may be used, although it should be stated that exercise capacity has been found to be the strongest predictor of mortality in the BODE index [58].

In 2011, GOLD introduced their own multidimensional composite measure, which included measures of airflow limitation, symptoms, and exacerbations in an ABCD classification [1]. The GOLD guidelines go on to acknowledge that comorbidities should be screened for, but to date have yet to be included in the assessment [1]. It wasn't until 2012 that a COPD specific comorbidity test (COTE index) was developed [39], and found that the addition of a comorbidities measure improved the prediction of BODE outcome even further (BODE+COTE index) [39, 59]. De Torres et al. [59] compared the BODE and the BODE+COTE with the ABCD GOLD classification, and found both BODE and the BODE+COTE superior to GOLD in predicting measures of prognosis outcome. Therefore, the ABCD GOLD classification is mainly a management tool and not necessarily used for prognostic purposes [59].

In general, composite measures have demonstrated superior ability than any individual measure

to predict outcomes such as mortality risk, hospitalizations, quality of life and depression [59]. The integration of composite measures is still under development; certain combinations of composite measures may be better than others. In future studies, other measures such as inflammatory markers could be added to the composite assessment to improve prediction further.

1.3 Circadian Rhythms and Diurnal Variations in Physiological and Psychological Functions

1.3.1 Defining diurnal variations

All biological processes follow an endogenous rhythm, which is a self-generating rhythm [60]. The human circadian (derived from latin, "*circa"* means "about" and "*dies"* means "day") rhythm is generated by an endogenous oscillator and follows an approximate 24-hour cycle [61]. On average, the period of the human endogenous rhythm has been estimated to be about 24.2 hours and may range from 23.5 to 24.5 hours [61, 62]. If they were to follow their own biological clocks, individuals would end up out of phase with the environmental 24-hour day. Therefore, the circadian rhythm needs to be synchronized to the environment. The suprachiasmatic nucleus (SCN), located in the anterior hypothalamus, is considered to be the mammalian master clock [63]. The SCN is thought to be the source of the endogenous rhythm; it synchronizes the circadian biological signals of peripheral clocks and entrains the systems to the environmental 24-hour day [60, 64]. Daily re-synchronization is needed, using exogenous inputs, to maintain entrainment between the endogenous rhythms and the environmental day. Light is the strongest environmental synchronizer used by the SCN [65]. Within the eye, rods, cones and specific retinal ganglion cells capture light, and this signal is sent along the retinohypothalamic tract, to be transmitted directly to the SCN [66, 67]. Exposure to the morning light can phase-advance circadian rhythms, whereas exposure to evening light produces a phase-delay [68]. Other synchronizers include the timing of rest or exercise, social exposure, and dietary intake, but with smaller effects than light exposure [60, 68]. Desynchronization may occur when the entrained rhythm is disrupted, or becomes out of phase with the environmental day, most commonly from transmeridian travel or night shift work but also from circadian or other disorders [69, 70]. Desynchronization may result in worsening health and well being [70]. Symptoms experienced may range from feeling tired, having poor concentration and memory, having changes in mood, digestive/gastrointestinal discomfort, nausea, etc. [70, 71]. Mounting evidence has been documenting the possible influence of circadian rhythm disruption in the development of chronic diseases, including cardiovascular disorders, metabolic disorders and cancer [71-74]. Perturbation of circadian entrainment has been shown to result in a reduction of circadian amplitude (assessed as half of the peak to trough cosine wave) in measures of endogenous rhythms (e.g.. melatonin, cortisol, etc.), which has been associated with negative health

outcomes [69]. Therefore, reduced circadian amplitude may also be an indicator of desynchronization.

Diurnal variations are the descriptive patterns of rhythmic changes that occur as a function of the endogenous circadian clock in addition to the influence of the external environment and behavioral cues over the period of 24 hours [61].

1.3.2 Diurnal variations in pulmonary function

Diurnal variability in airway resistance has been found in certain individuals with COPD [75-77]. Objectively measured diurnal variation from peak to trough in FEV_1 have been shown to exceed 200ml in COPD, which is comparable to the change after bronchodilation [75]. Teramoto et al. [78] conducted a study comparing pulmonary function at three different times of day as a function of age (comparing older and younger healthy participants) and presence of COPD (comparing COPD with healthy participants). No significant difference in daytime variation in expiratory flow was found as a function of age, between young and older participants. However, individuals with COPD had a significant difference from healthy individuals, with lower expiratory flow in the morning, and demonstrated greater coefficients of variation in daytime variation than the healthy individuals. This finding was in line with previous literature [79, 80]. Other causes of diurnal variability in respiratory measures in COPD may be related to changes in hyperinflation, which appears to be worst in the morning [7], and increased mucous secretions in the morning and evening [81]. Despite the evidence of variability in pulmonary variables in a subset of COPD patients, and recommendations to standardize the time of day for repeated pulmonary function testing [82], this has yet to be included in clinical practice guidelines.

Fluctuation in respiratory symptoms may be a reflection of changes to the airway caliber, or may be due to daily variations in physical activity, which increases symptoms of breathlessness [83, 84]. Nearly two thirds of symptomatic individuals with COPD report diurnal variability in symptoms such as breathlessness, cough, phlegm, chest tightness and wheezing [83, 85]. In COPD, respiratory symptoms appear to be worst in the morning [83-86].

Circadian variation have long been acknowledged in pulmonary function [87], but how these variations may be significant in clinical situations has not been given enough attention. In the assessment of pulmonary function, time of day is infrequently accounted for in research study designs and in clinical practice [88, 89]. Optimizing the timing of treatments could minimize periods of worse expiratory flow and symptoms [89]. Symptom variability may be another sign that the disease is not well controlled [84]. For example, individuals with greater variability in symptoms have been found to be more susceptible to frequent exacerbations [84]. Additionally, diurnal variability in breathlessness

has been shown to be associated with more severe dyspnea and may reflect greater severity of lung function decline, limitation to exercise, and more disturbed sleep [90, 91].

1.3.3 Diurnal variations in exercise capacity

In COPD, CPET is a useful means of assessment to objectively evaluate the cardiac, pulmonary, and musculoskeletal systems and their integrative responses [24]. Guidelines from the ATS and American College of Chest Physicians (ACCP) [24] advocate using the same time of day for repeated exercise evaluations in order to limit the confounding effect of diurnal variation in responses. The circadian rhythm of exercise performance has been hypothesized to follow the changes in body temperature rhythm (see Figure 3), with physiological variables related to exercise (ie. oxygen consumption (VO_2), carbon dioxide production (VCO_2) and heart rate (HR)) peaking in the afternoon [92-97]. Blood pressure (BP) generally seems to decrease at night but follows a pattern with two daytime peaks, one between 9:00h and14:00h, and the other at 20:00h with a dip at 16:00h, under resting conditions [98]. It can be difficult to determine physiological rhythms during exercise as different intensities can amplify, weaken, maintain or abolish responses [97, 99, 100].

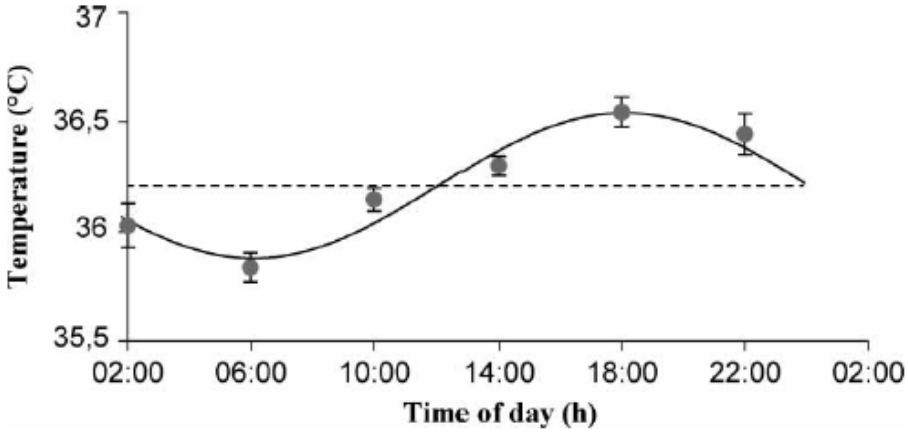

Figure 3 – Oral body temperature rhythm over 24 hours. Mean values (mean ± SD) with best-fit curve (cosinor analysis; solid line is the cosine curve and the dotted line is the mesor) [94].

When using exercise capacity as an outcome measure to evaluate the impact of treatments, it is important to know if changes are due to diurnal variations or to the intervention. Factors that may contribute to variability in exercise performance, and need to be controlled for in exercise testing protocols, include changes in clinical status, variability in symptoms, medication timing, and patient motivation. Results may be influenced by instructions, calibration errors and time of day [24]. The impact of time of day on the acute response to exercise has never been examined in COPD. Therefore,

further studies are needed in the area of diurnal variation and exercise capacity in COPD.

1.3.4 Diurnal variations in the rest-activity cycle

Circadian rhythms together with the homeostatic sleep drive are part of a two-process model, which regulate the sleep-wake cycle [101, 102]. Process C represents the endogenous control by the circadian pacemaker of the timing of sleep and wakefulness propensity, and process S represents the homeostatic need for sleep, which builds up the longer an individual remains awake and decreases the longer an individual is asleep (see Figure 4).

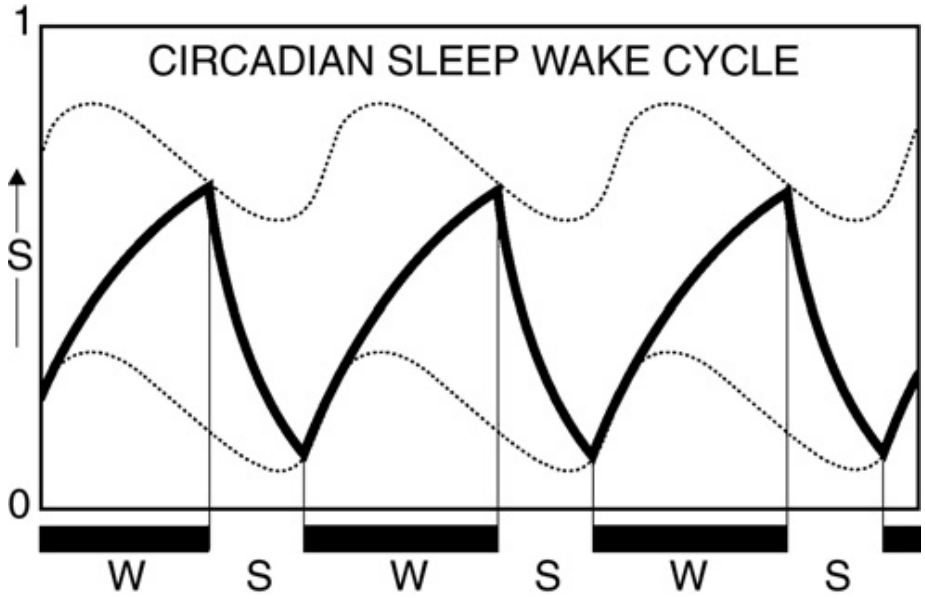

Figure 4 – Two-process model of sleep regulation [102]. Process S is the bold line increasing during W (wakefulness) and decreasing during S (sleep). Process C is the dotted line, which regulates the sleep-wake cycle within a range depending on time of day.

Sleep timing may be influenced by volitional decisions to wake up or to sleep earlier or later than usual, which can expose the endogenous circadian rhythm to exogenous influences like bright light at the wrong time of day, resulting in advancing or delaying phase [102]. Other influences may also be able to alter the pattern of rest and activity such as an individual's health condition [102]. Individuals with COPD are known to be more sedentary than their age-matched healthy counterparts, which may decrease the amplitude of the rest-activity cycle [103]. More specifically, with increasing COPD disease severity, physical activity frequency and duration decrease [104]. COPD symptoms such as dyspnea may also be a factor leading to decreased physical activity [105]. Greater sedentary behavior is strongly associated with increased comorbidities and mortality [106, 107]. As for sleep, approximately 50% of individuals with COPD complain of sleep problems [108]. In normal sleep there is a diminished respiratory center responsiveness, which also reduces the responsiveness of respiratory

muscles, increases airway resistance and mild nocturnal bronchoconstriction [91]. The contribution of accessory muscle is diminished, which changes rib cage positioning, and decreases functional residual capacity [91, 109]. These changes in respiration during sleep can lead to hypoventilation, hypoxemia, and hypercapnia, this response may be exaggerated within individuals already burdened by respiratory limitations as with COPD [91, 109]. This decrease in respiratory center responsiveness can lead to a lack of oxygen, which may manifest itself into disruptive symptoms causing individuals to wake up. Respiratory symptoms, such as coughing, wheezing, and dyspnea may cause disruptions during sleep [91]. Respiratory symptoms have also been found to significantly increase the probability of taking daytime naps [110]. Greater sleep fragmentation has been associated with greater odds of napping [110]. As both daytime activity levels and nighttime sleep quality may be disturbed in COPD patients, a disruption in the rest-activity cycle seems likely. As daytime activity decreases and nighttime activity increases, the amplitude of the rest-activity is diminished.

The rest-activity cycle can be described using various parameters including relative amplitude (RA), an indicator of the internal synchrony between physiological function and the endogenous circadian rhythm, intradaily variability (IV), a measure of fragmentation of the diurnal rhythm, and interdaily stability (IS), an index which categorizes the amount of synchronization with the environmental day-night cycle [111, 112]. Relative amplitude is the most commonly reported parameter. Currently, no accepted threshold has been determined to describe normal levels of amplitude. Values obtained in an older group of healthy individuals (n = 23, mean age = 64 ± 5 years) for RA ranged between 0.77 and 0.96, with a median of 0.91 [113]. The IS index can range from a value of 0 to 1, with 1 being a perfect coupling of the internal rhythm with environmental cues and 0 showing more day-to-day variation [112, 114]. The IV score ranges from 0 to about 2, a score near 0 represents a perfect sine wave where the subject is active during the day and asleep at night, to values of 2 or more, indicating high fragmentation, i.e. a large amount of transition between rest and activity [112]. In a study of 1734 healthy older adults (mean age = 62 ± 9 years) the mean IS was 0.80 ± 0.10 and the IV was 0.42 ± 0.13 [115].

It has been hypothesized that disruption of the rest-activity cycle may be reflective of anomalies in the circadian functions of the biological clock. Such circadian disruption, especially low circadian amplitude, has shown associations with more severe disease severity and worst prognostic outcome in many medical conditions, including cancer [116], Alzheimer disease [117, 118], and cardiovascular disorders [119]. Limited literature has investigated the relationship between IS and IV measures and chronic disease. A sample of Schizophrenia participants [113] when compared to healthy older participants [115] had a lower IS value, possibly indicating worst coupling with the environmental

cues, and higher IV value, possibly indicating more fragmentation of the rest-activity cycle. To our knowledge, the association between the rest-activity cycle and disease severity and prognosis has not been investigated in COPD.

1.3.5 Diurnal variations in psychological distress

Changes in mood, such as with mood swings, are present even in healthy individuals [120, 121]. The overall pattern of diurnal variation of mood in healthy individuals seems to follow the endogenous rhythm of core body temperature [94, 120, 121]. When assessing the circadian rhythm of mood, the lowest values usually occurred during the night. In studies investigating sleep, it has been found that even slight changes in sleep timing can modify mood, even in healthy individuals [122]. A shift of sleep timing can affect synchronization of circadian phase [122]. After forced desynchronization, the pattern of diurnal mood variation is similar to that observed with depression. Depressed individuals have demonstrated a pattern of lowest circadian mood around the time of awakening, several hours after the pattern observed in healthy individuals [121, 122]. As poor sleep is a symptom of depression, the role of sleep may be inextricably related to depressive mood variations [122]. Poor sleep is also a symptom found in COPD, and individuals with overlapping symptoms of sleep and depression with COPD may also demonstrate the pattern of lowest circadian mood in the morning.

It has been hypothesized that reduced circadian amplitude may be part of the pathogenesis of depression [123]. If the circadian rhythm becomes desynchronized then the risk of instability in depressive symptoms response may occur. In individuals with greater diurnal variation in symptoms of depression have reported more severe depression severity [124]. It would be interesting to investigate if the same were true in clinical populations such as with COPD where assessing depression can be difficult. Previous studies have investigated depressive mood states using positive and negative affect measures [125, 126] or using questionnaires that rely on recall of depressive symptoms [124]. Moullec et al. [127] developed a four-item questionnaire, which assessed symptoms of depression including, positive and negative affect, somatic complaints and disturbed interpersonal relationships. This short questionnaire was designed for ecological momentary assessment (EMA), the questionnaire is short, self-administered, repeatable and uses momentary sampling [128]. To our knowledge, no study has used such an instrument to explore the relationship between diurnal variation in the course of depressive symptoms and depression symptom severity.

2.0 RATIONALE, OBJECTIVES & HYPOTHESES

COPD is a complex disease, which does not solely affect the lungs but may limit systemic function (ie. skeletal muscle function), psychological function (causing psychological distress), and behavioral function (ie. sleep and physical activity). Our entire system is controlled by circadian rhythms, and patterns of diurnal variations have been observed in clinical measures of pulmonary function, exercise, sleep-wake cycle, and psychological distress. However, these patterns of diurnal variations have not been investigated in a COPD population. Therefore, the overarching goal of my thesis is to investigate the relationship between diurnal variations and the above-mentioned clinical assessment measures in COPD. Understanding the influence diurnal variations play in chronic diseases, such as COPD, could help in its management and treatment.

Data from the research project was organized and analyzed to meet three main objectives.

Objective #1:

The ATS/ACCP guidelines for CPET advocate using the same time of day for repeated testing so as to limit diurnal variation in response [24]. However, the recommendation was drawn from a sample of healthy individuals [129]. Based on the literature in healthy individuals, exercise seems to follow the circadian rhythm of body temperature, which peaks in the afternoon [94]. However, other factors may have an impact on exercise capacity in COPD. A common limitation to exercise is symptoms of dyspnea [130]. Dyspnea has demonstrated a diurnal pattern, being more pronounced in the morning [83, 84]. The cardiopulmonary response to exercise is an integrative measure of the major systems, and determining how time of day may impact exercise in COPD remained to be investigated. Therefore, we aimed to investigate the effect of time of day in pulmonary function and exercise capacity in COPD patients.

Specific Aim:

Evaluate the effect of time of day on peak exercise capacity (watts), resting pulmonary function (FEV_1, FVC), resting and peak physiological responses (VO_2, HR, VCO_2, BP, etc.), and resting and peak perception of symptoms (dyspnea and leg fatigue) in COPD patients.

Hypotheses:

It was hypothesized that a diurnal effect of time of day would elicit greater exercise capacity in the afternoon, along with greater physiological response to exercise, with the exception of the measure

of blood pressure, which would be greater in the morning. Pulmonary function was expected to be lower in the morning along with greater symptom perception occurring in the morning.

Objective #2:

A larger amplitude of circadian rhythms has been found to be associated with lower disease severity and better outcome in multiple pathologies [116-118, 131]. A larger circadian amplitude may be an indicator of better internal synchronization of the circadian rhythms [71]. The rest-activity cycle is a validated, non-invasive, measure of circadian rhythmicity, which has been used in previous studies to assess circadian amplitude [116-118, 131]. To our knowledge, the relationship between circadian amplitude and severity of disease and prognosis had yet to be investigated in COPD. Bromundt et al. [113] used a median split to compare Schizophrenia patients with high- or low-amplitude of their rest-activity cycle to evaluate a possible association with their cognitive function. We used a similar approach to investigate disease severity and prognosis outcomes in COPD patients with high or low amplitude of their rest-activity cycle.

Specific Aim:

Compare COPD severity and prognosis indexes between patients with high and low relative amplitude of the rest-activity cycle. Evaluate daytime activity levels and indicators of sleep quality to determine their contribution to high and low relative amplitude of the rest-activity cycle in COPD.

Hypotheses:

It was hypothesized that COPD patients in the low amplitude subgroup would have increased severity of disease and worst prognosis as compared to the high amplitude group. Compared to the low amplitude subgroup, the higher amplitude group was expected to have both higher activity levels during the day and a more consolidated sleep during the night.

Objective #3:

Individuals with reduced exercise capacity and lung function have been shown to present more symptoms of depression [46, 49, 132]. Depression is a common comorbidity in COPD and the development of either of the diseases may be interrelated [41, 45]. Due to common symptoms between COPD and depression such as poor sleep and fatigue, presence of psychological distress specifically due to depression is difficult to assess in COPD patients. Morris et al. [124] found that greater diurnal

variation in depression symptoms was associated with worst depression severity in otherwise healthy individuals. Therefore, evaluating the depressive symptoms variability might be of use in patients with COPD to estimate the depression severity. To our knowledge this approach had yet to be investigated in clinical populations. Furthermore, the assessment of diurnal mood variation has traditionally been evaluated with questionnaires, which relied on recall of symptoms in the past days, weeks, or more. The optimal evaluation of diurnal mood variation would be to utilize an ecological momentary assessment (EMA) methodology [128]. The EMA approach assesses what an individual is feeling or doing at that moment in time and reduces the risk of recall bias [128]. Using an EMA approach may be a useful method to facilitate the identification of more severe depression symptomatology.

Specific Aim:

Investigate whether depression symptom severity had an association with diurnal variation in depression symptoms in COPD patients. Verify if functional limitations due to COPD (FEV_1, FEV_1/FVC ratio and peak work rate) explained the possible relationship between depressive symptom severity and diurnal mood variations in COPD patients.

Hypotheses:

It was hypothesized that COPD patients with more severe depression would demonstrate greater diurnal variation in depressive symptoms and that COPD related functional limitations would influence the relationship between depressive symptom severity and diurnal mood variations.

3.0 METHODS

3.1 Participants

Participants were recruited at Hôpital du Sacré-Coeur de Montréal via recruitment flyers, doctor referrals, from a collective database of individuals who were agreeable to be contacted for research purposes and from personal contacts. To be eligible for the study, the participants had to be 40 years or older, had a smoking history of at least 10 American pack years (20 cigarettes per pack), be diagnosed with at least moderate disease severity with a post-bronchodilation FEV_1 less than 80% of the predicted normal value and FEV_1 to FVC ratio less than 0.7, and had previous experience with exercise testing. Participants were ineligible for the study if they did not have clinically stable COPD, had an exacerbation in the past four weeks (defined as a change in respiratory symptoms like dyspnea, volume or colour of sputum, treated with antibiotics or systemic corticosteroids, or were hospitalized), had any

contraindication(s) to exercise testing based on the ATS/ACCP guidelines [24], had any active condition other than COPD that could influence their exercise capacity (for example, unstable coronary heart disease, left congestive heart failure, neoplasia, severe claudication, severe arthritis, etc.), or if they were being treated with O_2 therapy and were prescribed Theophylline. The eligibility criteria were meant to differentiate COPD from other respiratory diseases and to ensure clinical stability and patient safety. Eligibility criteria was verified by consulting patient medical dossiers and by questioning patients upon recruitment.

3.2 Research Design and Procedure

Interested eligible participants were invited to the respiratory research laboratory at Hôpital du Sacré-Coeur de Montréal where the project was explained in detail and the participants' questions to the research protocol answered. Informed consent was acquired, in accordance to the hospital ethics committee standards, and medical clearance obtained prior to participation. With their respirologist collaboration, participants prescribed a long-acting anticholinergic agent (tiotropium) were substituted to a short-acting anticholinergic agent (ipratropium bromide) 40 μg QID (quarter en die, or four times a day) two weeks prior to the start of the research project and throughout the period of the study. In order to limit the effect of respiratory medication on diurnal variation in measured outcomes, prescribed pulmonary medications were withdrawn for a short period before undertaking the repeated pulmonary and exercise test. The withdrawal period before the evaluations was six hours for short acting β2-agonists, short-acting anticholinergic agents, combination products of short-acting agents, and 24 hours for long acting β2-agonists, inhaled corticosteroids, and combination of long-acting agents.

A total of four hospital visits were planned for the study and each visit lasted one to two hours and the last three visits were separated by at least 36 hours. The initial visit included baseline assessments and a familiarization of the pulmonary function and exercise capacity assessment. At visits 2 – 4, participants performed a spirometry test followed by a symptom-limited cycle ergometer test at three different times of day (8:00, 12:00, and 16:00), each on a different visit. The evaluation times were chosen to reflect the range of hours when tests are conducted in clinical practice. A counterbalanced assessment schedule, using six different combinations of times, was used to limit an order effect. However, scheduling order was subject to change due to medical supervision and patient availability.

At the first visit, the participants were given a journal to keep track of their sleep, activity, depressive symptoms, compliance with medications and dietary intake throughout the period of the

study. See the Appendix for a copy of the journal. Participants were also equipped with an accelerometer and kept track of their compliance to wearing the accelerometer in their journals. At the last visit the journal and accelerometer was collected, and participants returned to their normally prescribed medication regime.

3.3 Measures

3.3.1 Anthropometric measurements

At baseline, height was measured in meters; participants were instructed to remove their footwear and to stand with their back straight against a stadiometer and their weight was measured in kilograms using a digital scale (Digital beam scale, DS50100). The same scale was used for each participant. The body mass index (BMI), was calculated as a ratio of weight divided by the height squared (kg/m^2). The BMI categories were as follows; underweight if values were <18.5, normal if values were between 18.5 and 24.9, overweight if values were between 25 and 29.9 or obese if values >29.9 [133, 134].

3.3.2 Pulmonary function test

Pulmonary function was assessed using a spirometry test and was performed using cardiometabolic equipment (Jaeger, Oxycon Pro, Care Fusion, Germany). The equipment was first calibrated to ensure quality and reproducibility of measures. An initial demonstration of the pulmonary function manoeuver was given and the test procedure explained before each evaluation. The test was conducted with the participant seated and equipped with a nose clip and mouthpiece with a flow volume sensor (TripleV) connecting to the cardiorespiratory circuit. A minimum of three normal tidal breaths was recorded and at the end of a normal exhalation, the participants were encouraged to take a rapid, complete, maximal inhalation. Without hesitation the participants were encouraged to exhale forcefully and fully, until no further air could be expelled. Finally, a full maximal inhalation was taken. The manoeuver was repeated to obtain three acceptable tests; repeatability between tests was achieved when differences were ≤ 0.15 L for FEV_1 and FVC values [19]. If the repeatability was not achieved within three maneuvers, additional tests were conducted to a maximum of eight possible manoeuvers in accordance with ATS/ ERS guidelines [19]. The FEV_1 is the volume of air expired in the first second of forceful expiration and the total volume of air expired is the measure of FVC. The FEV_1 and FVC values were obtained from the best of the three acceptable manoeuvers. The absolute values of FEV_1 and FVC were measured in liters, in addition to being normalized for changes in age, sex and height using the predicted normal values from the European Community for Coal and Steel/ERS [18]. The

percent ratio of FEV_1 to FVC was also calculated, as it is the main diagnostic criteria in COPD and together with FEV_1 % predicted assures the presence, stability and severity of disease. The minimal clinical important difference (MCID) for FEV_1 was estimated to be between 100-150 mL, and for FVC between 150 – 325 mL [19, 135, 136].

3.3.3 Exercise testing

A symptom limited incremental cycling exercise test was conducted to determine peak exercise capacity in accordance to the ATS/ERS guidelines [24]. The participants were seated on the electromagnetically-braked cycle ergometer (Ergoselect 200P, Ergoline, Germany) and outfitted with a facemask connected to the cardiorespiratory circuit through the digital volume sensor to continuously record measures of VO_2, VCO_2, $V_{T,}$ respiratory exchange ratio (RER), minute ventilation (VE), and respiratory rate (RR). Pulse oximetry (SpO_2) was also obtained continuously along with a 12-lead electrocardiogram (Jaeger Oxycon Pro, Care Fusion, Germany) to determine HR. Every other minute an IC maneuver was performed and BP (Tango, SunTech Medical, USA), dyspnea and leg fatigue (modified 10-point Borg scale [137]) were assessed.

The testing procedure was explained to participants before each evaluation. The first five minutes were spent at rest, seated on the cycle ergometer, to obtain baseline measures. The participants then did a warm-up, pedaling at a rate of at least 50 revolutions per minute, without any workload, for three minutes. Every minute thereafter, the workload increased in stepwise increments of 5 to 10 watts, up until maximum capacity was reached. Increments were determined based on prior exercise capacity: if < 50 watts, 5-watt increments were used and 10-watts if ≥ 50 watts. Peak exercise capacity (W_{peak}) and peak oxygen capacity (VO_{2peak}) were obtained when the highest work rate was achieved and a pedaling speed of at least 50 revolutions per minute for a minimum of 30 seconds was maintained [24]. W_{peak} was assessed in watts and VO_{2peak} were expressed as a percent of the predicted normal, based on age, sex and weight, and calculated using Hansen's equation [138]. A 10-watt change has been identified as the MCID for exercise capacity [139].

3.3.4 Psychological distress

The Center for Epidemiological Studies Depression Scale (CES-D), the French version [140], is a 20-item questionnaire which was administered at the initial visit. Participants were asked to assess the frequency of depressive symptoms in the past week using the 4-point Likert scale from a score of 0 to 3. The total score can range from 0 to 60, with a larger score signifying greater depressive symptomatology.

In the journal, the very short version of the CES-D (VS-CES-D) [127] was included and participants were instructed to complete the questionnaire at three time points during the day: in the morning, afternoon and evening. The VS-CES-D was a 4-item questionnaire comprising a measure of positive affect ("I am happy"), depressed affect ("I have crying spells or feel like it"), disturbed interpersonal relationships ("I feel that people dislike me") and somatic complaints ("I talk less than usual"). Participants were asked to mark a vertical line through the 100 mm visual analogue scale indicating how their depressive symptoms appear to them at that moment, from a range of "not at all" to "absolutely". The VS-CES-D utilizes an EMA approach and has excellent psychosometric properties [127]. Confirmatory factor analysis models were conducted to test the validity of the four items version with the full CES-D version and a moderate to satisfactory reliability coefficient was obtained; 0.79 for positive affect, 0.87 for depressed affect and somatic complaints, and 0.67 for interpersonal relationships [127]. A fifth VAS scale was used and serve as an error measure, participants were asked to mark the mid-point of the 100 mm line. A randomized order for each of the items, and a different page for each time of day, was used in the journal. The amplitude of the diurnal variation in psychological distress was calculated from the difference between the maximum and the minimum daily score from the VS-CES-D and averaged over the seven days.

3.3.5 Rest-activity cycle

Rest-activity measures were obtained through acccelerometry, a measure of body movements that is then digitized into a measure of activity counts. The Actiwatch-2 (Mini-Mitter/Respironics, Bend, OR, USA) is a multi-axial accelerometer, worn throughout the study on the non-dominant wrist like a watch and set to measure one-minute epoch lengths, 24 hours per day for a minimum of seven consecutive days. The Actiwatch-2 sensitivity is 0.025 g, with a bandwidth between 0.35 to 7.5 Hz (typical) with a sampling rate of 32 Hz. After the period of data collection, the Actireader downloads the information to a computer and the Actiware software version 5.7 (2012 Koninklijke Phillips Electronics N.V.) was used to digitize and analyze data. Data was cleaned based on information reported in the journals on any removal of the actiwatch, the related data was removed so as to not be confused with periods of no activity. Missing data was removed, based on criteria previously established by Tabak et al. [141] who eliminated the entire hour if more than half of the data is missing. Van Someren et al. [112] went further to define zero movement or a consistent value with no change over the period of an hour as missing data, and finally if three or more hours per day is considered missing, the entire day was removed [113]. Non-parametric circadian rhythm analyses were carried out to obtain measures of relative amplitude, interdaily stability and intradaily variability [111, 112].

Relative amplitude was calculated on the average 24-h profile and is the ratio of the difference between the 10 most active and 5 least active hours over the sum of the 10 most and 5 least active hours. A larger amplitude demonstrated a greater contrast in day-night activity and a more pronounced rhythm. Van Someren et al. [112] described the equations to calculate interdaily stability and intradaily variability. Interdaily stability is a measure of day-to-day variability and measures the strength of the rhythms synchronization with external environmental cues. Intradaily variability measures the fragmentation of the rest-activity rhythm throughout a 24-hour period, that is, the frequency of transition between rest and activity [111, 112].

3.3.6 Sleep

Measures of sleep were obtained from the Actiwatch and sleep journal. The Actiwatch was equipped with an event marker button, and participants were instructed to press the event marker at bedtime, when ready to sleep, and again in the morning upon waking up. Bedtime and wake time, identified visually from actigraphic data, were corroborated using the event marker data as well as the reported bedtime and wake time from the sleep journal data. The sleep journal was completed daily and included data on the previous night's sleep quality, assessed on a Likert scale from 1 being very bad to 5 being very good sleep, and a measure of alertness upon waking, with 1 being very tired and sleepy to 5 being awake and energetic.

Wrist actigraphy is a validated measure (96.5% sensitivity and 86.3% accuracy against the gold standard polysomnography) for the assessment of sleep [142]. The Actiware software estimates bed and wake time, sleep onset latency (time between bed time and sleep onset), snooze time (time between last awakening and identified wake time), sleep duration (time in bed – sleep onset latency – snooze), wake after sleep onset (WASO), total sleep time (TST) (sleep duration – WASO) and sleep efficiency (TST/ sleep duration x 100).

3.3.7 Comorbidities

Information on comorbidities were obtained from the patients' medical dossier at the same time as when the participant's eligibility was being determined for the study. At the initial visit, information obtained from the participant was used to confirm and update any additional comorbidities. Comorbidities were scored using the COTE index designed specifically for COPD [39]. Twelve identified comorbidities have been found to be related to increased mortality risk; oncologic (lung, pancreatic, esophageal and breast cancer), pulmonary (pulmonary fibrosis), cardiac (atrial fibrillation/flutter, congestive heart failure, coronary artery disease), gastrointestinal (gastric/duodenal

ulcers, liver cirrhosis), endocrine (diabetes with neuropathy), and psychiatric (anxiety) [39]. A score can range between 0 and 25 and a value > 4 has been associated with a greater risk of mortality [39]. The C statistic for the COTE index was 0.66 for its ability to predict mortality [39].

3.3.8 Composite measure of outcome

The modified BODE index (mBODE%), is a multidimensional grading system which combines measures of Body composition, airflow Obstruction, Dyspnea, and Exercise capacity and has been shown to be a better predictor of mortality than FEV_1 alone in COPD patients [48, 56]. Body composition and airflow obstruction were assessed at the initial visit as previously described. The measure of dyspnea was obtained within six months of the baseline assessment from patient's medical dossiers prior to taking part in the study. Respirologist routinely measure dyspnea using the mMRC dyspnea scale [22, 143]. The mMRC dyspnea scale is a five-point scale, which corresponds to statements related to physical activity and level of breathlessness as follows; "*Grade 0: breathless with strenuous exercise, Grade 1: short of breath when hurrying on level ground or walking up a slight hill, Grade 2: walked slower than people of the same age on level ground, and experienced breathlessness or the need to stop to breathe when walking on level ground a their own pace, Grade 3: stop to breathe after walking about 100 yards or after a few minutes on level ground, and Grade 4: too breathless to leave the house, or breathless when dressing and undressing"* [22]. Exercise capacity was calculated as the average VO_{2max}% predicted obtained from the three incremental cycle ergometer tests. The BODE index has a total possible score ranging from 0 to a maximum of 10, with a greater score indicating an increased risk of death [48]. Each of the individual items in the index is attributed a point value, if BMI is > 21 a score of 0 and if ≤ 21 a score of 1, airway obstruction (FEV_1%predicted) if ≥ 65% a score of 0, 50-64% a score of 1, 36-49% a score of 2, and if ≤ 35% a score of 3, dyspnea index if grade 0-1 a score of 0, grade 2 a score of 1, grade 3 a score of 2 and grade 4 a score of 3, and exercise capacity (VO_2%predicted) if >70% score of 0, 60-69% score of 1, 40-59% score of 2, <40% score of 3 [48, 144]. The C statistic for the BODE index was 0.74 for its ability to predict the risk of death [48].

Finally, the aggregated measure of BODE and COTE, has been shown to improve the predictability of mortality than if the measures were assessed alone [39, 59]. The C statistic for the BODE+COTE index was 0.79 in its ability to predict mortality [39].

3.4 ANALYSES

Analyses #1:

The effect of time of day (8:00, 12:00 and 16:00) on peak exercise capacity and pulmonary function were compared using one-way repeated measure analyses of variance (ANOVA). If findings were significant a pairwise Bonferronni correction was applied to identify where the differences occur. A 2 x 3 repeated measures ANOVA compared the effect of time of day and state (resting and peak) for measures of physiological response and symptom perception. The Friedman test was used for any non-parametric data. To test the presence of an order effect for the tests, the first and last session values were compared using a t-test. Within-subject variability was assessed over the three testing sessions with an estimate of the coefficient of variation ([standard deviation / mean] x 100), the average amplitude of change (Δmax-min), and the percent variation [(Δmax-min/min) x 100]. Analyses were conducted to identify individuals who had clinically important differences in all three primary outcome measures (W_{peak}, FEV_1 and FVC) according to the suggested MCID. Individuals were divided into subgroups of high and low diurnal variability and were compared for the variables of age, sex, BMI, exercise capacity and pulmonary function using a t-test. Repeated measures ANOVA were conducted in each of the subgroups to determine if there is a time of day effect in pulmonary function or peak exercise capacity.

Analyses #2:

Using the same methodology as Bromundt et al. [113], a median split for relative amplitude was used to determine high and low amplitude. Independent Student's t-tests compared the high or low amplitude group on measures of disease severity and prognosis. Data was grouped into 3-hour bins and repeated measures analysis of variance (2 x 8 ANOVA) analyzed the differences by time and between high and low amplitude goups. Degrees of freedom were adjusted with Huynh-Felt correction for repeated measures. The analysis of covariance (ANCOVA) was applied on significant results to control for the potential effect of age.

Analyses #3:

After verifying for normality, a Pearson or Spearman rank correlation test were used to assess the relationship between depression symptom severity, measured with the CES-D questionnaire, and amplitude of diurnal variation in the EMA psychological distress measures. Correlation tests also explored the functional limitations in COPD patients (i.e., FEV_1, FEV_1/FVC, W_{peak}) in relationship with depression symptom severity and variability in depressive symptoms.

4.0 RESULTS

4.1 Article #1: Clinical impact of time of day on acute exercise response in COPD

Title:

Clinical Impact of Time of Day on Acute Exercise Response in COPD

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Abstract

The purpose of this pilot study was to determine the impact of time of day on the acute response to incremental exercise in chronic obstructive pulmonary disease (COPD).

Fourteen subjects (nine men) aged 71 ± 7 years with moderate to severe airflow obstruction (FEV_1: 58 ± 13% predicted) followed a counterbalanced randomized design, performing three symptom-limited incremental cycling tests at 8:00, 12:00, and 16:00 hours on different days, each preceded by a spirometry. COPD medications were withdrawn prior to testing.

No overall time effect was found for peak exercise capacity ($p = 0.22$) or pulmonary function (FEV_1, $p = 0.56$; FVC, $p = 0.79$). However, a large effect size ($f = 0.48$) was observed for peak exercise capacity and several pulmonary function parameters. For peak exercise capacity, the average within-subject coefficient of variation was 5.5 ± 3.9% and the average amplitude of change was 7 ± 5W. Seven subjects (50%) showed diurnal changes at levels equal to or beyond the minimal clinically important difference for both peak exercise capacity and pulmonary function. In this sub-group, peak exercise capacity was greatest at 16:00 hours ($p = 0.03$, $f = 1.04$).

No systematic time-of-day effect on peak exercise capacity was obtained in COPD patients in the present pilot study. However, based on the observed effect size and on the average amplitude of change and within-subject variations seen across testing times, the guidelines recommendation that time of day be standardized for repeat exercise testing in COPD should be maintained.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive and partially irreversible disease associated with frequent changes in clinical status [145]. Within a single day, lung function and symptom perception have been shown to vary [79, 82, 83]. In patients with COPD, who are sensitive to small increases in airway obstruction, diurnal variations in physiological parameters are likely to have important functional repercussions [89].

Cardiopulmonary exercise tests measure the global and integrative response of the major systems and provides exclusive information above what is found from resting measures alone [24, 146]. Current exercise testing guidelines in COPD recommend that repeated exercise tests be undertaken at the same time of day to avoid the potential confounding effect of circadian variations in exercise measures [24]; yet this recommendation is based on findings in healthy individuals [129]. In COPD, the impact of time of day on exercise performance remains to be examined.

The primary objective of the present pilot study was to evaluate the effect of time of day on peak exercise capacity in COPD. Secondary objectives were to evaluate the effect of time of day on i) resting pulmonary function, ii) resting and peak physiological responses, and iii) resting and peak symptoms perception (dyspnea and leg fatigue).

METHODS

Subjects

Subjects were recruited from Hôpital du Sacré-Coeur de Montréal between August 2010 and April 2011 from a pool of patients who had completed previous studies in our laboratory and had consented to be contacted for future investigations. Eligibility criteria included: 1) clinically stable COPD; 2) aged 40 years or older; 3) smoking history of at least 10 American pack-years (20 cigarettes per pack); 4) post-bronchodilation forced expiratory volume in 1 second (FEV_1) less than 80% of the predicted normal value; 5) FEV_1 to forced vital capacity (FVC) ratio less than 0.7; and 6) previous experience of exercise testing. Exclusion criteria were: 1) respiratory exacerbation in the past 4 weeks (change in dyspnea or volume/colour of sputum, need for antibiotic treatment, or hospitalization); 2) contraindication to exercise testing based on guidelines from the American Thoracic Society (ATS) [24]; 3) active condition other than COPD that could influence exercise tolerance; 4) need for oxygen therapy; and 5) prescribed theophylline. The research protocol was approved by the institutional ethics committee and a signed informed consent was obtained from each subject.

Study design and procedure

Subjects obtained medical clearance and came to the research facility for a total of four visits. The first visit included collecting demographic and clinical information (age, sex, height, weight, and body mass index (BMI)), baseline spirometry, and a familiarization with the testing equipment and procedure.

Subjects then entered the counterbalanced design (visits 2-4) where they each completed a spirometry followed by a symptom-limited incremental cycling exercise test, each conducted on a different day, at a different time (08:00, 12:00, and 16:00 hours ± 15 min). The selected testing times were chosen to cover the range of hours when exercise tests are typically conducted in clinical practice. Study visits were separated by at least 36 hours, but no more than 1 week. To limit a potential training effect, the order of testing times was determined through block randomization; however, participant availability and accessibility to medical supervision were considered. To limit the potential confounding effect of the timing of COPD medications on exercise capacity at different times of day, subjects were asked to withhold their respiratory medications 6 to 24 hours before visits 2-4 (Table 3). All other pharmacological treatment remained unchanged and subjects returned to their original regimen upon completion of their last study visit.

Assessments

Pulmonary function testing

Spirometry was performed at baseline and before each evaluation according to recommended techniques [19]. Values were compared to predicted normal values from the European Community for Coal and Steel/European Respiratory Society (ERS) [18].

Exercise testing

The symptom-limited incremental cycling exercise test was selected as it is currently the most frequently used in respirology [147]. Subjects were seated on an electromagnetically braked cycle ergometer (Ergoselect 200P, Ergoline, Germany) and connected through a mouthpiece to a cardio-respiratory circuit which consisted of a digital volume sensor (TripleV), oxygen and carbon dioxide analyzers, and 12-lead electrocardiogram (Jaeger Oxycon Pro, CareFusion, Germany). After five minutes of rest followed by three minutes of unloaded pedalling, the workload was increased in a stepwise manner every minute, up to the individual's maximum capacity. The workload was increased by 5 or 10 watt (W) increments (5 W for subjects with a predicted peak work rate < 50 W; 10 W for those with a predicted peak work rate > 50 W, as determined from each subjects previous experience

with exercise testing). Gas exchange parameters (minute ventilation ($\dot{V}_E$), oxygen consumption (VO_2), and carbon dioxide production ($\dot{V}CO_2$)), pulse oximetry (SpO_2), and heart rate (HR) were measured at rest and during exercise on a breath-by-breath basis. Blood pressure (BP) (Tango, SunTech Medical, USA), inspiratory capacity (IC) (in accordance to the ATS/ERS guidelines [19, 148]), and dyspnea and leg fatigue (modified 10-point Borg scale [137]) were measured at rest and every other minute during exercise. Peak exercise capacity was defined as the highest work rate maintained at a pedalling speed of at least 50 revolutions per minute for a minimum of 30 seconds. All tests were completed under medical supervision.

Special attention was taken to optimize reproducibility of measurements as outlined in the ATS and American College of Sports Medicine (ACSM) guidelines [24, 134]. Prior to each evaluation, the cardiometabolic equipment and gas analyzers were calibrated. Laboratory temperature (22.2 ± 0.6°C) and humidity (37.6 ± 14.6%) were maintained within recommended ranges for all tests. Instructions given to participants followed the ACSM guidelines [134], encouragement during the test were standardized, and all tests were conducted by the same two exercise physiologists.

Statistical analyses

To verify the distribution of normality for the primary and secondary outcomes, measures of skewness and kurtosis were used. For our primary objective, the overall effect of time of day (08:00, 12:00 and 16:00 hours) on peak exercise capacity was assessed with one-way repeated-measures analyses of variance (ANOVAs) using the General Linear Model. If a significant effect was obtained, pairwise comparisons with Bonferroni's corrections were conducted to identify time points showing significant differences. For our secondary objectives, we did the same analyses for parametric data, and Friedman tests were performed for non-parametric data. To test the presence of a potential order effect, results from the first and third sessions were compared using paired t-tests. Within-subject variability over the three testing sessions was estimated with the coefficient of variation (standard deviation [SD]/mean x 100), the average amplitude of change (Δmax-min), and the percent variation ([Δmax-min/min] x 100).

Subjects showing changes at or beyond the suggested minimal clinically important difference (MCID) were identified for peak exercise capacity (MCID of 10 W [139]), FEV_1 (MCID between 100-150 ml [19, 135]), and FVC (MCID between 150-325 ml [19, 136]) . Exploratory a posteriori analyses were conducted to characterize subjects with clinically important variations on all three outcomes. More specifically, these subjects – which were considered as having high diurnal variability – were compared

to the remaining subjects (low variability) on age, sex, BMI, exercise capacity, and pulmonary function using t-tests for independent samples. In the subgroup with high diurnal variability, a repeated-measures ANOVA was conducted to test the presence of a time-of-day effect.

Huynh-Feldt correction was applied for analyses on more than two levels, but original degrees of freedom are reported. The effect size was calculated for each statistical test according to established methods [149] and categorized as small (≤ 0.1), medium (= 0.25), or large (≥ 0.4). Statistical tests were two-tailed and conducted at the 5% level of significance. They were performed with SPSS version 18.0 (Chicago, IL).

RESULTS

Subjects

Fourteen subjects (nine men) accepted to participate and completed all measurements. Baseline characteristics of the study group are presented in Table 4 and are representative of moderate to severe disease in subjects with COPD.

Overall diurnal variations

Individual results and group means for peak exercise capacity are shown in Figure 5. There was no statistically significant effect of time of day for peak exercise capacity measured at 08:00, 12:00 and 16:00 hours (mean ± SD wattage of 72.5 ± 18.3, 75.0 ± 17 and 75.4 ± 17.6, respectively) ($F_{2,26}$ = 1.61, p = 0.22), but the effect size was large (f = 0.48). There was no effect of testing order, based on the comparison between the first and last exercise tests (t_{13} = -0.19, p = 0.85, d = 0.02).

Individual data and group means for FEV_1 and FVC values obtained at rest prior to each exercise test are shown in Figure 6. No significant effect of time of day was detected for FEV_1 ($F_{2,26}$ = 0.59, p = 0.56, f = 0.27), FVC ($F_{2,26}$ = 0.24, p = 0.79, f = 0.19), or the ratio of FEV_1/FVC ($F_{2,26}$ = 0.08, p = 0.92, f = 0.11).

Group means for resting and peak $\dot{V}_E$, respiratory rate (RR), tidal volume (V_T), IC, VO_2, $\dot{V}CO_2$, respiratory exchange ratio (RER), SpO_2, HR, and BP are shown in Table 5. A significant effect of time of day was observed for RER under resting conditions ($F_{2,26}$ = 8. 64, p = 0.005, f = 1.16); resting RER was higher in the morning than at the other two time points. A trend for a time-of-day effect was detected for resting V_T ($F_{2,26}$ = 2.75, p = 0.08, f = 0.62), which tended to decrease over the course of the day. Finally, a trend was also found for the effect of testing time on peak HR ($F_{2,26}$ = 3.26, p = 0.08, f = 0.68), which tended to increase throughout the day.

Subjects' ratings of dyspnea and leg fatigue increased from rest to peak ($p < 0.001$ for both), but no time effect was found for either measure (Table 6).

Within-subject variability

For peak exercise capacity, the average within-subject coefficient of variation was 5.5 ± 3.9% (range, 0 to 11%), the average amplitude of change was 7 ± 5 W (range, 0 to 10 W), and the average percent change was 10 ± 7% (range, 0 to 20%). Nine out of the 14 subjects showed a change beyond the suggested MCID of 10 watts for peak exercise capacity between the different testing times.

The average within-subject coefficient of variation in FEV_1 was 4.8 ± 3.5% (range, 0 to 13%), the average amplitude of change was 0.12 ± 0.10 L (range, 0.02 to 0.43 L), while the average percent change was 9 ± 6% (range, 1 to 22%). The average within-subject coefficient of variation for FVC was 14% ± 7.8% (range, 4 to 23%), the average amplitude of change was 0.6 ± 0.3 L (range, 0.1 to 1.2 L), with a corresponding percent change of 22 ± 11% (range, 2 to 36%). Nine of the 14 patients (64%) showed a variability ≥ 100 ml in FEV_1 between visits, while three subjects showed changes ≥ 150 ml. Twelve of the 14 subjects (86%) showed a variability ≥ 150 ml in FVC between visits, and 10 subjects (71%) showed changes ≥ 325 ml.

Exploratory analyses on subgroups having high or low diurnal variability

In seven of the 14 subjects (50%), diurnal variability exceeded the lowest suggested MCID value in all three measures; peak exercise capacity, FEV_1 and FVC. These subjects were identified as having high diurnal variability and exploratory analyses were conducted to characterize this sub-group compared to the seven with lower diurnal variability, using t-tests for independent samples. There was no significant difference for age, sex, exercise capacity, or pulmonary function (FEV_1, FVC, FEV_1/FVC, IC). The only significant difference was for BMI ($t_{12} = -2.30$, $p = 0.04$, $d = 1.23$), which was greater in subjects with high diurnal variability. In the sub-group showing high diurnal variability, repeated-measures ANOVA were conducted to test the presence of a time-of-day effect. For these subjects, peak exercise capacity increased over the day ($F_{2,12} = 3.80$, $p = 0.05$, $f = 1.04$) from 08:00 (74.3 ± 15.1 W) to 12:00 (78.6 ± 16.8 W) to 16:00 hours (81.4 ± 13.5 W), with a significant difference between 08:00 and 16:00 hours ($p = 0.03$). No significant time-of-day effect was detected for FEV_1, FVC and FEV_1/FVC in this sub-group.

DISCUSSION

This pilot study was designed to investigate the effect of time of day on incremental exercise testing measures in COPD patients. Standardization of exercise testing times is recommended in the ATS guidelines [24], yet this study is the first, to our knowledge, to investigate diurnal variability in exercise performance in a COPD patient population. Though not statistically significant, the size of the effect of time of day on peak exercise capacity was large [149]. Resting RER was greatest in the morning than at the other two time points. No significant time-of-day effect was detected for pulmonary function or symptom perception.

Within-subjects variability

The within-subjects variability across the three times of day was relatively high, as shown by a mean coefficient of variation of 5.5%. According to the ATS/ACCP guidelines for cardiopulmonary exercise testing [24], this value falls within the range reported in reproducibility studies of peak exercise capacity in COPD patients (3.7 to 13.8%). However, the studies cited in the guidelines were conducted more than 20 years ago [150-154] when both methodologies and equipment were likely less reliable than those available today. A recent well-designed study using modern equipment found a coefficient of variation of 2.3% for repeated measures maximal incremental cycle tests conducted at the same time of day within a period of eight to 10 days in 10 COPD patients [155]. Therefore, the variation of 5.5% measured in the present study suggests that variability of the results increases when the tests are conducted at different times of day.

In addition to the coefficient of variability, the average amplitude of change can be used to compare time-of-day effects against those of widespread treatments. For example, pulmonary rehabilitation has been shown to elicit an average improvement (common effect) of 5.5 W (95% CI: +0.5 to 10.2 W) in peak exercise capacity in moderate to very severe COPD [156], while bronchodilation has been associated with changes ranging up to 7 W [157]. In the present study, peak exercise capacity varied, on average, by 7 ± 5 W, with a range of 0 to 10 W across the 14 subjects. Therefore, our results show that, in some patients with COPD, the amplitude of diurnal variations in peak exercise capacity associated with different testing times can exceed the amplitude of changes expected with bronchodilation and even pulmonary rehabilitation. Consequently, even if there was no systematic time-of-day effect in our group of subjects, the guidelines recommendation to repeat exercise testing at the same time of day should be maintained, as diurnal variations may have clinically significant effects in certain patients with COPD.

In the present study, subjects were instructed to refrain from ingesting food within 3 hours of testing, in accordance to guidelines from the American College of Sports Medicine [134]. However, based on patient-reported information on time since last dietary intake, the interval between the last intake and the exercise test was shorter for the morning test as compared to the other time points. This may explain why resting RER was greatest in the morning. Indeed, prior food intake has been shown to increase RER values, but not peak exercise capacity, in a healthy population [158]. Together, these findings highlight the importance of standardizing instructions given to participants prior to an exercise test.

Between-subject variability in light of classification of the subjects according to recommended MCID values

An important observation made in this pilot study was the heterogeneity in the amplitude of variations in subjects' response to tests conducted at different times of day. To explore potential differences between subjects showing high or low diurnal variability, they were classified according to previously suggested MCID values for peak exercise capacity [139] and resting pulmonary function (FEV_1 and FVC) [19, 135, 136]. The MCID is the smallest clinical difference in a measure that can either be perceived by the patient or that is believed to be clinically pertinent by expert opinion [159]. Interestingly, most subjects showing diurnal variations equal or larger than the MCID for peak exercise capacity also showed clinically significant changes for resting pulmonary function. These subjects showing high diurnal variations on all three measures constituted exactly half of our sample (seven of 14 subjects).

When the sub-groups showing high or low diurnal variability were compared, no difference emerged for disease severity or for average exercise capacity. Age, gender and smoking status were also evenly distributed in the two sub-groups. The only significant difference was for BMI, which was higher in the sub-group showing more diurnal variability. The clinical significance of this observation will have to be determined. A higher BMI – which may reflect better preserved muscle mass – has been shown to have a protective effect on lung function decline in individuals at risk of developing COPD and to predict better survival in those suffering from COPD [160-162]. The diurnal maximum observed at 16:00 hours for peak exercise capacity in patients with high diurnal variability is similar to the peak observed in circadian rhythms in healthy subjects for measures of exercise performance such as peak oxygen consumption [95] and exercise heart rate [95, 96, 163]. This observation suggests that this diurnal maximum is not a random variation but may rather reflect a circadian rhythm of larger amplitude in patients with high variability. A larger amplitude may result from a better internal

synchrony between underlying physiological functions [71] and, as in other pathologies [116, 117, 131], high variability may therefore predict a better clinical outcome in COPD patients. This hypothesis cannot be confirmed with only three time points and in the absence of independent circadian measures. Future studies will be needed to determine whether the combination of high diurnal variability and high BMI could be used to define a specific phenotype of patients and predict clinically meaningful outcomes such as symptom exacerbations, progression of disease and response to therapy [160]. These studies should include a precise measurement of body composition (e.g. duel energy x-ray absorptiometry) to assess the relative contribution of muscle and fat mass in this potential phenotype.

Strengths, limitations, and perspectives

To our knowledge, this study is the first to address diurnal variations in peak exercise capacity in patients with COPD. It was conducted with the highest methodological standards, including carefully calibrated equipment and standardized procedures. To limit a potential training effect, all selected subjects had previous experience with testing procedures, and the testing order for the three times of day was counterbalanced across the subjects. In addition, great care was taken to avoid direct effects of the timing of COPD medication in relation to exercise testing, as all COPD medications were withdrawn at least 6 hours before each testing session.

This study was a pilot study and its main limitation is the modest sample size. The large effect size found for time of day on peak exercise capacity suggests that significant results may emerge in a larger group of subjects. A larger group would also allow for the characterization of potential sub-groups based on time of day variability. The diurnal maximum observed at 16:00 hours for peak exercise capacity suggests a larger circadian amplitude in patients with high variability. This hypothesis cannot be confirmed with only three time points and in the absence of a valid circadian marker. Further studies will be needed to confirm if greater variability can indeed predict better outcome in COPD. Finally, MCID estimates were used in exploratory analyses to identify subjects in whom clinically significant changes were observed across the three times of day. The limitation of using MCID estimates as cut-off thresholds to dichotomize individuals as “responders” or “non-responders” after an intervention has been demonstrated [164]. However, in the absence of a reproducibility criterion for peak exercise capacity, the MCID was deemed the alternative of choice. Caution is nonetheless warranted in the interpretation and generalization of these findings.

CONCLUSION

No systematic time-of-day effect on peak exercise capacity was obtained in COPD patients in the present pilot study. However, our findings on the average amplitude of change and within-subject variations seen across testing times support the guidelines recommendation to standardize time of day for repeat exercise testing in patients with COPD. The presence of high or low diurnal variability in peak exercise capacity needs to be further investigated to examine its potential clinical significance.

Declaration of interest

The authors report no financial, consulting or personal relationships that have influenced their work.

Table 3 – Medication restrictions before visits 2, 3, and 4

Type of Medication	Name of Medication	Restriction
Short-acting β2-agonists	Salbutamol (Ventolin, Airomir, Apo-Salvent) Terbutaline (Bricanyl)	6-hour withdrawal
Short-acting anticholinergic agents	Ipratropium bromide (Atrovent)	6-hour withdrawal
Combination products of short-acting agents	Salbutamol/ipratropium (Combivent)	6-hour withdrawal
Long-acting β2-agonists	Salmeterol (Serevent) Formoterol (Oxeze)	24-hour withdrawal
Inhaled corticosteroids	Fluticasone (Flovent, Flonase) Budesonide (Pulmicort) Beclometasone dipropionate (Clenil, Qvar)	24-hour withdrawal
Combination products of long-acting β2-agonists and inhaled corticosteroids	Fluticasone/salmeterol (Advair) Budesonide/formoterol (Symbicort)	24-hour withdrawal
Long-acting anticholinergic agents	Tiotropium (Spiriva)	Switched to short-acting anticholinergic agent 2 weeks prior to study, then 6-hour withdrawal

Table 4 - Demographics and baseline characteristics of the 14 subjects (9 men, 5 women)*

Age, yrs	71 ± 7
Height, m	1.70 ± 0.08
Weight, kg	78.2 ± 14.8
BMI, kg/m^2	27 ± 5
FEV_1, L	1.48 ± 0.40
FEV_1, % pred.	58 ± 13
FVC, L	2.83 ± 0.64
FVC, % pred.	87 ± 17
FEV_1/FVC, %	53 ± 11

*Values are mean ± SD

BMI: Body mass index, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity.

Table 5 – Physiological response (mean ± SD) at rest and at peak exercise capacity at the three testing times. Results of the analysis of variance on time of day, as well as the calculated effect size (***f***) are also shown.

Physiological Measure	**08:00**	**12:00**	**16:00**	$F_{2,26}$	***p***	***f***
V_E rest, L	11.8 ± 2.0	11.6 ± 2.7	11.3 ± 3.1	0.60	0.49	0.29
V_E peak, L	40.6 ± 8.8	41.8 ± 7.4	42.0 ± 8.9	0.55	0.58	0.28
RR rest, L/min	16.4 ± 5.3	18.0 ± 5.1	18.4 ± 3.2	1.30	0.29	0.43
RR peak, L/min	32.4 ± 5.8	32.2 ± 5.9	33.2 ± 4.8	0.91	0.41	0.36
V_T rest, L	0.93 ± 0.40	0.80 ± 0.39	0.70 ± 0.27	2.75	0.08	0.62
V_T peak, L	1.28 ± 0.24	1.34 ± 0.33	1.28 ± 0.27	1.52	0.24	0.46
IC rest, L	2.24 ± 0.33	2.33 ± 0.62	2.39 ± 0.50	1.19	0.32	0.41
IC peak, L	1.65 ± 0.37	1.67 ± 0.58	1.70 ± 0.37	0.09	0.91	0.36
VO_2 rest, ml/kg/min	3.6 ± 0.6	3.6 ± 1.2	3.4 ± 0.8	0.46	0.64	0.26
VO_2 peak, ml/kg/min	13.7 ± 3.3	14.4 ± 2.8	14.1 ± 3.0	1.73	0.20	0.50
VCO_2 rest, ml/min	250 ± 51	233 ± 80	224 ± 64	1.65	0.22	0.49
VCO_2 peak, ml/min	1057 ± 281	1102 ± 275	1086 ± 289	0.75	0.48	0.33
RER rest	**0.90 ± 0.06***	**0.84 ± 0.06**	**0.83 ± 0.05**	**8.64**	**0.005**	**1.16**
RER peak	0.99 ± 0.11	0.99 ± 0.10	1.00 ± 0.12	0.19	0.83	0.12
SpO_2 rest, %	97 ± 1	97 ± 1	97 ± 1	0.05	0.95	0.09
SpO_2 peak, %	95 ±1	95 ± 2	95 ± 2	0.14	0.87	0.14
HR rest, beats/min	78 ± 7	77 ± 6	80 ± 8	1.36	0.28	0.44
HR peak, beats/min	112 ± 11	114 ± 11	117 ± 11	3.26	0.08	0.68
BP systolic rest, mmHg	114 ± 23	121 ± 14	121 ± 22	1.04	0.37	0.39
BP systolic peak, mmHg	176 ± 27	183 ± 27	173 ± 20	2.08	0.15	0.54
BP diastolic rest, mmHg	75 ± 7	74 ± 7	77 ± 11	0.78	0.43	0.33
BP diastolic peak, mmHg	80 ± 13	78 ± 9	81 ± 13	0.37	0.61	0.23

* Significantly different from the other two time points, $p < 0.05$.
VO_2 = oxygen consumption, VCO_2 = carbon dioxide production, RER = respiratory exchange ratio, V_E = minute ventilation, RR = respiratory rate, V_T = tidal volume, SpO_2 = oxygen saturation, BP = blood pressure.

Table 6 – Symptoms (mean ± SD) of perceived dyspnea and leg fatigue as measured by the modified 10-point Borg scale at the three testing times.

Symptoms	**8:00**	**12:00**	**16:00**	**Chi-Square**	**df**	***p***
Dyspnea rest	0.4 ± 0.6	0.2 ± 0.4	0.1 ± 0.4	3.13	2	0.21
Dyspnea peak	6.0 ± 2.4	6.0 ± 2.3	6.0 ± 1.9	0.05	2	0.98
Leg fatigue rest	0.1 ± 0.4	0.0 ± 0.0	0.1 ± 0.3	3.71	2	0.16
Leg fatigue peak	6.0 ± 2.3	6.0 ± 1.9	6.0 ± 2.2	1.22	2	0.54

df = degrees of freedom

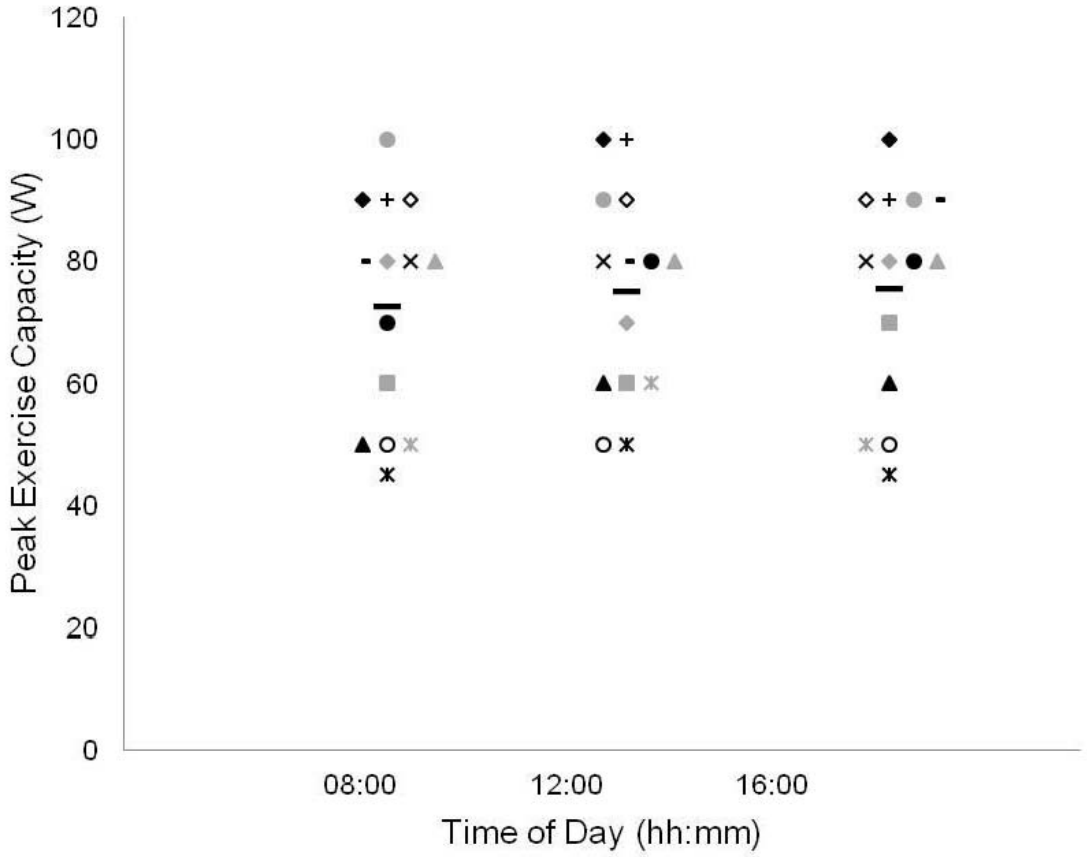

Figure 5 - Peak exercise capacity at the three testing times. Each subject is identified by a specific symbol. Group means are represented by black horizontal bars.

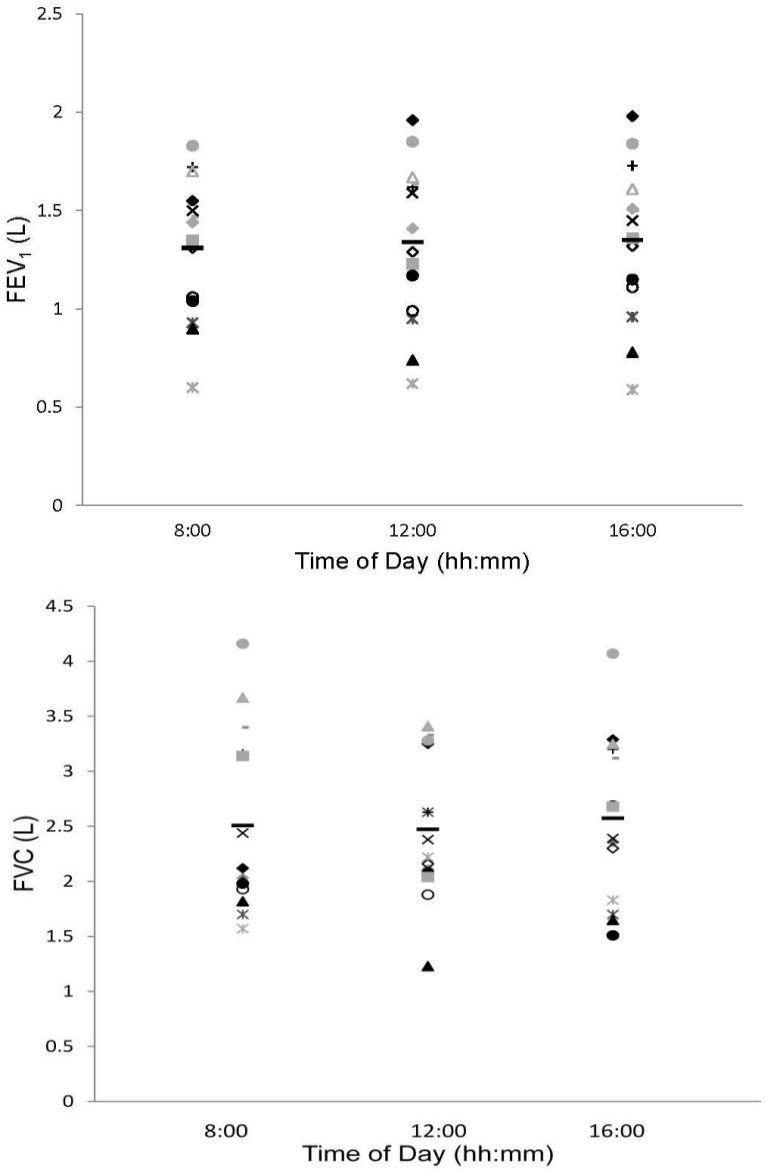

Figure 6 – Individual data for forced expiratory volume in one second (FEV_1) (upper panel) and forced vital capacity (FVC) (lower panel) at the three testing times. Each subject is identified by a specific symbol. Group means are represented by black horizontal bars.

4.2 Article #2: Amplitude of the rest-activity cycle in chronic obstructive pulmonary disease

Title:

Amplitude of the rest-activity cycle in chronic obstructive pulmonary disease

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Running Header: Rest-activity cycle in COPD

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ABSTRACT

In Chronic Obstructive Pulmonary Disease (COPD), there is a large individual variability in the progression of the disease. Low amplitude of rest-activity rhythms has been associated with worse prognosis in a variety of diseases, but it has not been investigated in COPD. The first aim of this exploratory study was to compare disease severity and prognosis indicators between COPD patients having relatively high or low amplitude of their rest-activity cycle, as measured with actigraphy. As a second objective, both 24-h profiles of activity levels and nighttime sleep quality were compared between the two sub-groups to assess the relative contribution of day and night activity levels to high and low rest-activity rhythm amplitude in this population. Rest-activity rhythms were measured with 8 to 14 days of wrist actigraphy in 14 patients (9 men), aged 58 to 79 years, suffering from moderate to severe COPD. Relative amplitude (RA) of 24-h activity profiles ranged from 0.72 to 0.98. Participants were divided at the median into high-amplitude (mean ± SD: 0.90 ± 0.04) and low-amplitude (0.79 ± 0.05) sub-groups. There was no significant difference between the two sub-groups for pulmonary function and exercise capacity. However, the low-amplitude group had more severe symptoms of dyspnea and worse prognostic scores than the high-amplitude group ($p < 0.05$). The 24-h activity profiles revealed higher levels of activity in the high-amplitude group for the 12:00 to 15:00 h interval ($p < 0.05$). There was no significant difference between the two groups for subjective or actigraphic estimates of sleep quality, sleep duration or proportion of daytime sleep. This exploratory study is a first step towards the identification of larger rest-activity rhythm amplitude as a marker of better prognosis in COPD and as another potential target for exercise-based rehabilitation programs in this population.

INTRODUCTION

Studies in a variety of medical disorders, including cancer,[116] Alzheimer's disease [117, 118] and hypertension,[131] have found that a larger amplitude of the rest-activity rhythms is associated with lower disease severity and better prognosis. Rest-activity rhythms were usually measured with continuous actigraphic recordings, a technique that has the advantage of being non-invasive and providing results that are representative of patients' usual behaviour. In a recent review, Truong et al[165] clearly demonstrated the impact of circadian rhythms in respiratory diseases. However, their review also highlighted the scarcity of literature on this topic in Chronic Obstructive Pulmonary Disease (COPD). To our knowledge, the association between amplitude of the rest-activity cycle and disease severity and prognosis has not been investigated in COPD patients.

COPD is a respiratory disorder that develops over time and is progressive by nature. It is a leading cause of morbidity and mortality worldwide[166]. The most common cause of COPD is the inhalation of noxious particles, like cigarette smoke. Airflow is obstructed by factors such as inflammation in the bronchioles, mucus hyper-secretion, and destruction of the lung parenchyma leading to the collapse of the alveoli and gas trapping in the lungs[167]. Destruction to the lungs cannot be reversed with current therapy; therefore the management of COPD aims to control symptoms and to slow down the progression of the disease [168]. The severity of COPD is traditionally measured by the degree of airflow limitation and by the presence of respiratory symptoms (dyspnea, cough, phlegm or wheezing), which have both been associated with increased mortality[169].

The progression of COPD is typically manifested by a decline of about 30 to 60 mL per year in forced expiratory volume in one second (FEV_1)[4, 170, 171]. However, the rate of

decline in lung function in COPD is not uniform and the progression of the disease is quite variable among patients. For instance, individuals who experience frequent exacerbations (>2 per year), a worsening of their respiratory symptoms usually caused by a respiratory infection, have demonstrated a faster rate of decline[172]. Life-threatening exacerbations have been associated with a phenotype that includes low body mass index (BMI), low exercise capacity, high dyspnea score and severe airflow obstruction. In this respect, a composite index combining these four indicators, the BODE index, has been developed and used as a good predictor of mortality risk in COPD patients[48]. The BODE index prognosis value is further improved when supplemented with a comorbidity index, the COmorbidity TEst (COTE) index, in which other conditions commonly associated with COPD (eg, cardiovascular disease, depression, sleep apnea) are integrated into a weighted score [39, 59].

In a study published in 2014[173], we reported the impact of time of day on exercise capacity in 14 COPD patients, studied using a counterbalanced repeated-measure design. Patients were evaluated three times over a period of 8 to 14 days during which they filled out sleep and mood diaries and underwent continuous actigraphic recordings. Mood data were published in 2016 [174]. For the present paper, we took advantage of the actigraphic data to explore the possible difference in disease severity and prognosis indexes between COPD patients having a relatively high or low amplitude of their rest-activity rhythms, with the expectation of finding lower severity and better prognosis in the subgroup of patients having a larger amplitude. We adopted the approach chosen by Bromundt et al.[113] who used the median amplitude to split a sample of schizophrenia patients into sub-groups having lower and higher amplitude of their rest-activity rhythms to compare their levels of cognitive functioning. As a second objective, actigraphic data were also used to compare profiles of 24-h activity levels and

indicators of nighttime sleep quality between the two subgroups to evaluate their respective contribution to high and low amplitude of rest-activity rhythms in this population.

MATERIALS AND METHODS

Participants

Fourteen patients with diagnosed COPD were recruited at the Hôpital du Sacré-Coeur de Montreal (HSCM) over an eight-month period. Recruitment was based on information reported in medical records. All patients were clinically stable and presented with moderate (n = 12) or severe (n = 2) airflow obstruction according to GOLD classification criteria [175]: post-bronchodilation FEV_1 less than 80% of the predicted normal value, and FEV_1 to forced vital capacity (FVC) ratio less than 70%. All patients were aged 40 years or older, had a smoking history of at least 10 American pack-years (20 cigarettes per pack), and had prior exercise testing experience. Exclusion criteria were: 1) a respiratory exacerbation in the past 4 weeks, as reported by the patient at recruitment and at the beginning of the study (change in dyspnea or volume/colour of sputum, need for antibiotic or systemic corticosteroid treatment, or hospitalization); 2) active condition other than COPD that could influence exercise tolerance; 3) need for oxygen therapy and 4) prescribed Theophylline. The local institutional ethics committee approved the research project and all participants signed an informed consent prior to taking part in the study. Detailed description of clinical characteristics and inclusion/exclusion criteria for the participants is provided in a previous publication [173].

Study design and procedure

Data presented in this paper were collected in a study evaluating the impact of time-of-day on the acute response to incremental exercise in COPD patients and detailed methodology

has been published in a previous publication [173]. Briefly, the study required four hospital visits and 8 to14 days of actigraphy and sleep-wake diary. At visit 1, BMI and baseline pulmonary function were measured, and depression and anxiety symptoms were assessed using the Center for Epidemiological Studies-Depression (CES-D) questionnaire [140] and the Beck Anxiety Inventory (BAI) [176] respectively. Visits 2 to 4 were scheduled at least 36 hours apart, included pulmonary function and exercise tests, and were identical except for the time of day (08:00 h, 12:00 h or 16:00 h). Patients were asked to withhold respiratory medications at least 6 hours before each visit. Ambulatory activity recording and sleep diaries were initiated at visit 1 and ended at visit 4. Comorbidities and dyspnea level were obtained from medical records.

Evaluation of disease severity

Three measures were used to assess COPD severity: a subjective measure of dyspnea, an objective measure of pulmonary function and a measure of peak exercise capacity.

Participant's level of dyspnea was obtained from medical records, as ascertained during the respirology appointment closest to the study (range 0 – 15 months, median: 1 month). It was measured with the modified Medical Research Council (mMRC) dyspnea scale [22, 177]. The mMRC dyspnea scale is a five-point scale that corresponds to statements related to physical activity and level of breathlessness as follows; Grade 0: breathless with strenuous exercise, Grade 1: short of breath when hurrying on level ground or walking up a slight hill, Grade 2: walked slower than people of the same age on level ground, and experienced breathlessness or the need to stop to breathe when walking on level ground at their own pace, Grade 3: stop to breathe after walking about 100 yards or after a few minutes on level ground, and Grade 4: too breathless to leave the house, or breathless when dressing and undressing [22].

Pulmonary function was assessed at visit 1 with spirometry, using cardiometabolic equipment (Jaeger, Oxycon Pro, Care Fusion, Germany). All patients were evaluated between 10:30 and 15:00 h. Spirometry was performed with the patient seated, as per recommended procedures [19]. At least two to three normal tidal breaths were taken followed by the manoeuvre where a full inspiration of air was immediately followed by a full and forceful expiration, until maximal expiration was reached. The total volume of air expired during the manoeuvre was recorded as the forced vital capacity (FVC) and the volume expired within the first second of the expiration was recorded as the forced expiratory volume in one second (FEV_1). The manoeuvre was repeated to obtain three acceptable tests and the best value obtained for FEV_1, FVC and the ratio of FEV_1/FVC was recorded. In addition to the absolute values, measures were normalized to account for differences in sex, age and height for a Caucasian population using the predicted normal values from the European Community for Coal and Steel/European Respiratory Society [18]. The resulting value of FEV_1%predicted was used to classify the severity of airflow obstruction.

Exercise capacity was evaluated at visits 2, 3, and 4 using an electromagnetically-braked cycle ergometer (Ergoselect 200P, Ergoline, Germany), with participants connected to cardiometabolic equipment (Jaeger Oxycon Pro, CareFusion, Germany). Participants performed symptom-limited incremental cycling exercise tests according to a standard protocol [147]. Testing began with five minutes of rest and three minutes of unloaded pedalling, and then the workload was increased in a stepwise manner by 5-10 watts every minute up to the individual's maximal capacity. Standardized instructions were given prior to each test and verbal encouragement given during the test was standardised at every 30 seconds. Maximal exercise capacity was recorded as the highest workload achieved and maintained for at least 30 seconds at

a pedalling rate of 50 revolutions per minute. Peak oxygen consumption (VO_2peak) was calculated for each test as the average VO_2 obtained over the last 30 seconds of the test. The mean of the results obtained at the three visits was then expressed as a percentage of the predicted normal value according to sex, age, and weight [138].

Evaluation of disease prognosis

Two measures were used to evaluate disease prognosis: the BODE index and the COmorbidity TEst (COTE) index. The BODE and COTE scores were also summed to form a composite score (BODE + COTE) which has been demonstrated to be a better predictor of mortality than the individual scores alone [39, 59].

The BODE index is a composite measure of body composition (B), airflow obstruction (O), dyspnea rating (D) and exercise capacity (E). The following elements account for the traditional BODE index: BMI as the measure of body composition, FEV_1 (% predicted) as the measure of airflow obstruction, mMRC score as the dyspnea rating, and distance walked on a 6-minute walk test as exercise capacity [48]. In the present study, a modified BODE index (mBODE%) was calculated, where percent VO_2peak was used as a measure of exercise capacity in replacement of 6-minute walking distance. This approach has been proposed and previously validated by Cardoso et al. [56]. Scores on the mBODE% index range from 0 to 10, indicating low to high risk of death respectively [48, 178].

The COTE index was calculated based on information reported verbally by the participant during the hospital visits and completed by a review of the participant's medical records. The COTE index categorizes comorbidities into 12 domains found to be associated with an increased risk of mortality in COPD patients [39]: oncologic (lung, pancreatic, esophageal and breast cancer), pulmonary (pulmonary fibrosis), cardiac (atrial fibrillation/flutter, congestive

heart failure, coronary artery disease), gastrointestinal (gastric/duodenal ulcers, liver cirrhosis), endocrine (diabetes with neuropathy), and psychiatric (anxiety). Each of these comorbidities is associated with a specific score. The final COTE score can range from 0 to 25 [59] and a score > 4 has been linked with an increased mortality risk [39].

Evaluation of the amplitude of the rest-activity cycle

Activity recordings were conducted with an actigraph equipped with an event marker (Actiwatch-2, Philips Respironics, Murrysville, PA, USA). The monitor was worn on the non-dominant wrist, 24 hours per day, for a minimum period of eight consecutive days (range: 8 to 14 days). Participants were instructed to press the event marker at bedtime, when ready to sleep, and at wake time in the morning. Periods of non-wear of the actigraph monitor (eg, for bathing, etc) were identified using the sleep-wake diaries and then excluded from the data. Further missing data were visually identified and removed based on the following published criteria: when more than 50% of the activity was missing per hour, the entire hour was excluded from the analyses [141] and when three or more hours were missing in the 24-h period, the entire day was excluded [113]. The mean of one-minute data was calculated for each valid hour of recording and then the one-hour means were averaged for each clock hour across the days of recording to obtain a 24-h profile.

To estimate amplitude of the rest-activity rhythm, we calculated the relative amplitude (RA), a non-parametric indicator that is not making assumptions about the shape of the rhythm [179]. The 10 consecutive most active hours of the day and the 5 consecutive least active hours of the night were identified from the 24-h profile. RA was then calculated as the ratio of activity during the 10 most active hours minus activity during the 5 least active hours over the sum of activity during the 10 most active and 5 least active hours.

Comparison of 24-h activity levels

Using the approach of Bromundt et al[113], activity counts were log-transformed and collapsed into 3-hour bins. Resulting profiles were then compared between the patients with higher and lower RA to determine the presence of differences between the two groups of patients.

Evaluation of nighttime sleep quality

One-minute actigraphic data were also used to estimate some indicators of nighttime sleep quality. Data were scored with the dedicated software (Actiware version 5.7, Philips Respironics, 2012) using a medium wake threshold (40 activity counts). For each data set, the actogram was visually inspected and compared with the participant-reported times via the event marker and sleep diaries. For each night of recording, bedtime and wake time were set using information from the sleep-wake diaries, data from the event marker, and visual inspection of the actogram. The interval between bedtime and wake time defined the duration of time in bed. Other variables were computed by the software and included 1) sleep latency (number of minutes between bedtime and sleep onset with sleep onset defined as the beginning of the first 10 consecutive minutes of sleep), 2) total sleep time (total number of minutes scored sleep), and 3) sleep efficiency (total sleep time divided by duration of the sleep episode x 100). Sleep efficiency was the main variable used as an objective estimate of sleep quality.

Sleep-wake diaries

On each day of ambulatory recording, participants filled a sleep diary to report bedtime and wake time, as well as presence and duration of daytime naps. These reports were used to calculate the subjective estimate of total duration of sleep per 24-h and the percentages of

daytime sleep in the total 24-h sleep. Subjective sleep quality was reported using a Likert scale from very bad (1) to very good (5) quality.

STATISTICAL ANALYSES

The 14 participants were split into two groups of 7 patients having higher or lower rest-activity rhythms amplitude, using the median RA as a threshold [113]. Data normally distributed were compared between the two groups using Student's t-tests. Analyse of covariance (ANCOVA) was used to control for age in comparisons yielding significant group differences. Comparisons of 24-h activity profiles were conducted using a group-by-time (2x8) analysis of variance (ANOVA) adjusted with Huynh-Felt correction for repeated measures (original degrees of freedom are reported). Results are presented as mean ± SD and level of significance was set at $p < 0.05$. Analyses were performed using SPSS version 23.

RESULTS

Participants

Participants included 9 men and 5 women aged 58 to 79 years (71 ± 7 y). Clinical characteristics of the fourteen participants are presented in Table 7. All participants had moderate to severe COPD and most had a moderate mMRC dyspnea index (index of 2). The average time since diagnosis was 5 ± 3 years and eleven (79%) participants were retired. All participants had previously been smokers and two (14%) remained active smokers. Twelve participants (86%) used short-acting anticholinergic medication at the time of the study. Nine of the participants (64%) used combination products of long-acting beta-2 agonists and inhaled corticosteroids.

Amplitude of the rest-activity rhythm and COPD severity and prognosis

The RA ranged from 0.72 to 0.98 (0.84 ± 0.07). The RA median split cut-off in our sample was 0.855. Mean RA was 0.79 (± 0.05) in the low-amplitude group and 0.90 (± 0.04) in the high-amplitude one. Comparisons of clinical variables between the two groups are presented in Table 8. Respiratory function (FEV_1%pred) and exercise capacity (VO_2max%pred) did not differ significantly between the two groups, but the low-amplitude group had more severe symptoms of dyspnea (mMRC score) and a worse prognosis according to COTE and BODE+COTE scores, compared to the high-amplitude group. There was no significant difference between the two groups for BMI.

Both age and psychological distress can influence clinical variables. Participants of the low-amplitude group were significantly older (75.0 ± 5.2 y) than participants of the high-amplitude group (67.9 ± 6.6 y; p= 0.04). When controlled for age using an ANCOVA, group differences remained significant for mMRC dyspnea score (p= 0.02) and BODE+COTE score (p= 0.049), but not for the COTE (p= 0.06). Psychological screening questionnaires yielded similar results between the two groups for depression (CES-D scores: 12.9 ± 10.3 *vs.* 11.3 ± 9.9 in low and high-amplitude groups, respectively; p = 0.78), and were not significantly different for anxiety (BAI scores: 10.4 ± 6.8 vs. 8.0 ± 7.2 in low and high-amplitude groups, respectively; p = 0.18).

Amplitude of the rest-activity rhythm and 24-h activity levels

The ANOVA showed no significant group effect ($F_{(1,12)}$= 0.86, p= 0.37) but the group-by-time interaction was significant ($F_{(7,84)}$= 2.53, p= 0.02). Simple-effect analyses revealed higher levels of activity in the high-amplitude group in the interval 12:00–15:00 h (p= 0.03), with a similar trend for the interval 09:00–12:00 h (p= 0.08). Results are illustrated in Figure 7.

Amplitude of rest-activity rhythm and sleep timing and quality

For each participant, reported sleep variables represent values averaged over 6 to 12 days of recording (mean of 9.1 ± 2.6 days). One participant from the low-amplitude group did not complete the sleep diary on all days; therefore subjective sleep quality and diurnal sleep to total 24-h sleep are available for only 13 subjects. On average, participants were in bed from 22:49 h (± 0:37) to 06:51 h (± 0:49), with a sleep onset latency of 22.3 min (± 17.8) and a sleep efficiency of 85.6% (± 6.8). Participants reported fair to good subjective sleep quality (range 3.17 to 4.31). Ten participants (77%) reported daytime naps with a mean duration of 49 ± 21 min.

Table 9 presents the comparisons of sleep variables between low- and high-amplitude groups. There was no significant group difference either for actigraphic measures or for subjective estimates of sleep timing and quality.

DISCUSSION

The main objective of this paper was to compare disease severity and prognosis indexes in COPD patients having a lower or higher amplitude of their rest-activity rhythm. Significant differences between sub-groups of low and high RA were found for dyspnea severity and for the combined prognosis score BODE+COTE, but not for respiratory function or exercise capacity. Differences were in the expected direction, with patients having a lower RA of rest-activity rhythms displaying greater symptom severity and worse prognosis.

There is currently no accepted threshold to determine a “normal” level of RA of rest-activity rhythms. However, using a median split to divide our group of patients into high- and low-amplitude sub-groups, we obtained a threshold of 0.855, similar to the threshold of 0.85 also found with a median split by Bromundt et al.[113] in their group of 14 middle-aged

schizophrenia patients. Moreover, the mean RA in our high-amplitude group (0.90) was similar to theirs (0.93) and was also similar to the median amplitude (0.91) they observed in an independent group of 23 healthy individuals slightly younger (64 ± 5.4 years) than our participants. In another study, a mean RA of 0.86 (± 0.02) was reported in 10 older (73 ± 1.5 y) healthy men [179]. RA higher than 0.85 seems therefore to be representative of healthier older individuals, but larger studies will be needed to determine a valid "normal" threshold in different age groups.

Many factors may contribute to decreased amplitude of rest-activity rhythms, an important one being older age [180, 181]. We did find that participants in the low-RA group were significantly older than those in the high-RA group. However, there was no significant difference in age between patients with moderate (mMRC score= 2; n= 8; age= 70.3 ± 7.3 y.) or severe (mMRC scores= 3-4; n= 6; age= 73.0 ± 6.4 y.) dyspnea symptoms (p= 0.48). Furthermore, group differences both in dyspnea score and BODE+COTE prognosis index remained significant when the effect of age was taken into account in ANCOVA analyses. Statistical control is very limited in this small number of subjects, but our results suggest that the age difference was not the main factor that explains the differences in dyspnea symptoms and prognosis between the two RA sub-groups. Among other factors previously associated with lower amplitude of rest-activity rhythms are high BMI [115] and symptoms of depression and anxiety [182-184]. In the present study, there was no significant difference between the high-RA and low-RA sub-groups for BMI nor for psychological distress evaluated with validated questionnaires. Because of the limited statistical power in this study, a contribution of these variables cannot be completely excluded, but they do not appear to be major factors explaining increased dyspnea symptoms and worse prognosis in the low-amplitude group.

Low amplitude of rest-activity rhythms may reflect disturbed nocturnal sleep and/or decreased daytime activity; both have been found to be associated with decreased amplitude in healthy aging [180]. Presumably in COPD, symptoms of breathlessness associated with severe dyspnea could result in more nighttime awakenings [91] and in turn reduce rest-activity amplitude by increasing nighttime activity. Other medical conditions associated with worse prognosis, as assessed with the COTE index, may also decrease nighttime sleep quality. However, sleep quality and total sleep time were not significantly different between our two sub-groups of high and low RA. In Bromundt et al. [113], with the same number of subjects, it was clearly greater nighttime activity that characterised their low-RA group ($p< 0.001$). In our group of COPD patients, the ANOVA rather identified lower daytime activity levels as the main factor contributing to low amplitude, especially at midday (Fig. 1). As our two sub-groups were very similar for total 24-h sleep time and proportion of daytime sleep (Table 3), increased napping in patients included in the low-RA group does not seem likely. Therefore, the amplitude difference between the two sub-groups appears to be due to increased physical activity at midday in the high-RA sub-group.

While a direction of causality cannot be established in this study, it can be hypothesized that patients with more severe symptoms of dyspnea and more comorbidities were more sedentary, leading to reduced levels of daytime physical activity and decreased amplitude of rest-activity rhythms. Indeed, reduced physical activity levels in COPD have been associated with increased dyspnea ratings on the mMRC[185], comorbid chronic illnesses such as heart disease and type 2 diabetes [186, 187], and a worse score on the BODE index[185, 188]. In our COPD patients, respiratory function (FEV_1%predicted) and exercise capacity (VO_2max%predicted) were not statistically different between low-RA and high-RA subgroups, suggesting that it was

not the severity of airflow obstruction that was restrictive for daytime activity. Symptoms of dyspnea were more severe in the low-RA subgroup. However, symptoms of dyspnea are usually worse in the morning [83, 84] and we observed differences in daytime activity mostly in early afternoon. Therefore, more than just symptoms of dyspnea may be influencing the amplitude of the rest-activity rhythm in our COPD patients.

Increased comorbidity in our low-RA group is consistent with reduced amplitude of the circadian rest-activity cycle reported in other disease conditions such as hypertension [131], cancer [116], and mood disorders [189], all conditions taken into account by the COTE index. In their study of schizophrenia patients, Bromundt et al. [113] found that low amplitude could be associated with disturbances of circadian rhythms as shown by a delayed onset of melatonin secretion in relation to sleep time, and they proposed that circadian desynchrony may explain the strong association they found between low amplitude and low scores on many tests of cognitive functions. There were no measures of endogenous circadian markers in the present study, but sleep timing and duration were in the normal range and were similar in the two amplitude sub-groups. Therefore, there was no indication of an abnormal circadian phase in the low-RA sub-group. The only indication of a possible circadian dysfunction is the lower RA. Low amplitude of the rest-activity rhythms has been found to be an independent prognostic factor for cancer patients' survival [184], suggesting the possibility of a two-way relationship between circadian amplitude and severity of clinical symptoms.

This study was an exploratory investigation of clinical differences between COPD patients with higher or lower amplitude of the rest-activity rhythm. This exploration was conducted on patients recruited for a broader study having different aims [173]. As such, the study presents some limitations, including a relatively small sample size and the absence of a

control group of age-matched healthy subjects. A larger sample would allow for the inclusion of a larger spread in disease severity, symptom ratings on the dyspnea scale, exercise capacity, and comorbidities, and would also allow for a more efficient control of possible mediators such as age, BMI and psychological distress. An age-matched control group would help to interpret differences in RA and to set boundaries for a normal range. Another limitation is that the dyspnea score was obtained at participants' medical visit closest to the study, which in two cases exceeded 6 months from the study visit. However, the mMRC is relatively insensitive to small changes in clinical status and to therapeutic intervention [190, 191]. Inclusion criteria required that only clinically stable patients were enrolled in the study; therefore the range in assessment time for the mMRC should not have had a significant effect on this measure.

Conclusions

This study is a first step towards the identification of larger rest-activity rhythms amplitude as a marker of better prognosis in COPD and as a potential target for exercise-based rehabilitation programs in this population [192]. Direction of causality cannot be determined in this study, but regular practice of physical activity may contribute to endogenous circadian amplitude and may have a synchronizing effect on circadian rhythms [179, 193, 194]. Beneficial effects of physical activity may therefore extend beyond increasing physical fitness, and positively impact on circadian physiology to improve quality of life and decrease mortality in COPD patients.

DECLARATION OF INTEREST STATEMENT

The authors report no potential conflicts of interest.

Table 7. Clinical characteristics of the 14 participants

Variables	Number or Mean ± SD	Range
COPD stage (II/III/IV)	12/1/1	II – IV
mMRC dyspnea score (2/3/4)	8/3/3	2 – 4
FEV_1 %predicted	58 ± 13	23 – 76
FEV_1/FVC (%)	53 ± 11	38 – 75
VO_{2max}%predicted	72 ± 14	46 – 96
BMI (kg/m^2)	27 ± 4	22 – 35
mBODE% index	3 ± 2	1 – 7
COTE index	1 ± 1	0 – 4
BODE + COTE	4 ± 3	1 – 8

FEV_1 : *Forced expiratory volume in one second.* FVC: *Forced vital capacity*. mMRC: *Modified Medical Research Council dyspnea scale.* VO_{2max}: *Maximal oxygen consumption.* mBODE: *Modified BODE index using VO_{2max}%pred.* COTE: *COPD specific comorbidity test*. BMI: *Body mass index*.

Table 8. Comparisons of clinical variables (mean ± SD) between participants with high or low relative amplitude of the rest-activity cycle

Variables	Low relative amplitude (< 0.855)	High relative amplitude (≥ 0.855)	P values
mMRC dyspnea score	3.14 ± 0.9	2.14 ± 0.38	0.026
FEV_1%pred	58.00 ± 7.77	57.71 ± 17.29	0.97
VO_2max%pred	67.40 ± 12.37	76.37 ± 14.86	0.24
BMI	28.8 ± 4.3	25.5 ± 3.6	0.15
mBODE% index	3.86 ± 1.57	2.43 ± 2.15	0.18
COTE index	1.71 ± 1.50	0.29 ± 0.49	0.046
BODE+COTE	5.57 ± 1.72	2.71 ± 2.43	0.026

mMRC: *Modified Medical Research Council dyspnea scale.* FEV_1%pred: *Forced expiratory volume in one second percent of predicted.* VO_{2max}%pred: *Maximal oxygen consumption percent of predicted.* BMI: *Body mass index*. mBODE% index: *Modified BODE index using VO_{2max}%pred.* COTE index: *COPD specific comorbidity test*.

Table 9. Comparisons of sleep variables (mean ± SD) between participants with high or low relative amplitude of the rest-activity cycle

Variables	Low relative amplitude (< 0.855)	High relative amplitude (≥ 0.855)	P values
Bedtime (h:m)	22:51 ± 00:25	22:48 ± 00:49	0.86
Wake time (h:m)	07:08 ± 00:54	06:34 ± 00:41	0.20
Time in bed (h)	8.3 ± 0.8	7.7 ± 0.9	0.24
Sleep latency (min)	24.5 ± 21.6	20.0 ± 14.6	0.65
Total sleep time (min)	382 ± 64	379 ± 63	0.95
Sleep efficiency (%)	82.8 ± 6.5	88.4 ± 6.2	0.13
Subjective sleep quality[a]	3.7 ± 0.4	3.9 ± 0.3	0.50
Total 24-h sleep (min)[a]	535 ± 65	511 ± 71	0.53
Diurnal /24-h sleep (%)[a]	6.76 ± 4.22	6.85 ± 5.55	0.98

[a]*Data from sleep diaries. Subjective sleep quality scored 1 (very bad) to 5 (very good).*

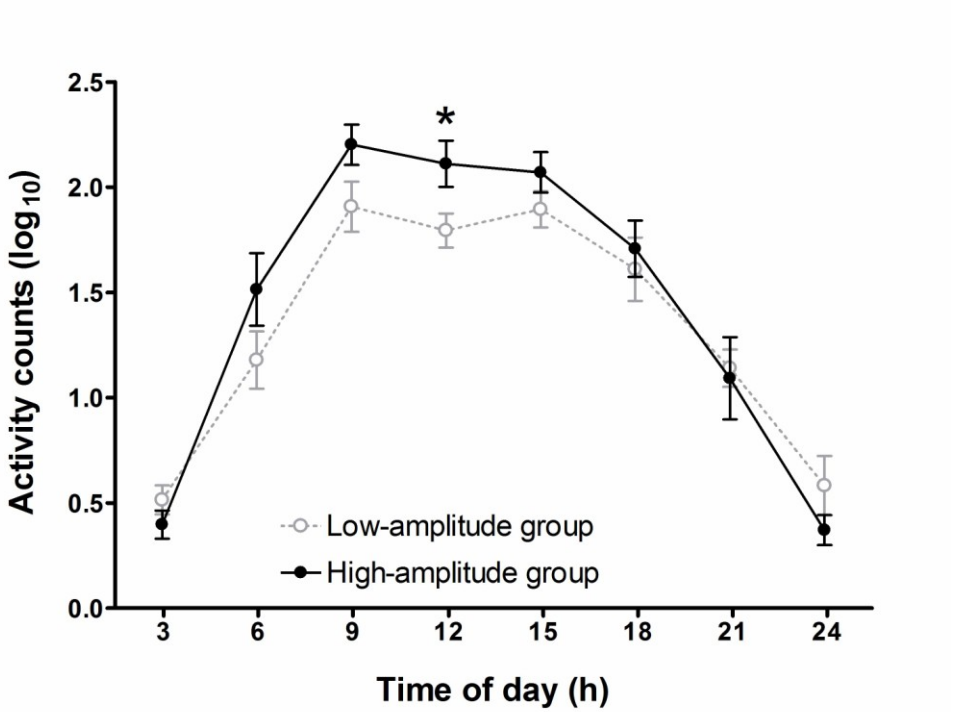

Figure 7. Activity counts (mean ± SD of log-transformed data) averaged for the next 3 hours (e.g. data reported at 3 h represents mean activity counts measured between 03:00 and 06:00 h), for the patients divided at the median into low and high relative amplitude groups (n= 7 in each group). Asterisk indicates significant group difference (p= 0.03), for the interval of 12:00 to 15:00 h.

4.3 Article #3: Diurnal variation in psychological distress in COPD

Title:

Diurnal Variation in Psychological Distress in COPD

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Keywords : Circadian rhythms; Chronic obstructive pulmonary disease; Depression; Diurnal variation; Psychological distress

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ABSTRACT

Purpose: Investigate the association between depressive symptoms severity and amplitude of diurnal variations in depression symptoms in patients with Chronic Obstructive Pulmonary Disease (COPD).

Design: Prospective**,** observational proof-of-concept study

Methods: Fourteen participants with moderate/severe COPD completed a 20-item Center for Epidemiologic Studies Depression scale (CES-D) estimating depressive symptoms severity. Throughout 1-week, the 4-item very short version of the CES-D was completed every day in the morning, afternoon, and evening.

Findings: Strong positive correlations were observed between depressive severity and the mean range of diurnal variations in positive ($r = 0.61$) and depressed affects ($r = 0.67$), somatic complaints ($r = 0.82$) and disturbed interpersonal relationships ($r = 0.71$).

Conclusion: In COPD patients, a greater diurnal variation in depression symptoms was associated with greater depression severity. This relationship seems independent of COPD severity.

Clinical Relevance: Diurnal variation of symptoms of depression is a new method of identifying depression severity in COPD.

Key Practice Points:

- Depression is a highly prevalent comorbidity in COPD, but is under recognized and may be due to an overlap in shared symptoms of COPD and depression.
- A defining feature of depression is diurnal variation, however past assessments have all relied on recall methods rather than ecological momentary assessments.
- Using an ecological momentary assessment method, greater amplitude in diurnal variation was found to significantly correlate to more severe depression, independent of COPD disease severity.
- The use of a brief assessment to evaluate diurnal variation in depressive symptoms may be a highly relevant marker to clinicians in identifying more severe depression in COPD.

INTRODUCTION

Recent updates to the management guidelines for COPD [195] acknowledge the importance of depression as a highly prevalent comorbidity, which is still under diagnosed and under treated [44]. The overlap between functional symptoms of COPD and depression (*e.g.*, fatigue and poor sleep) increases the challenge of estimating depression severity in patients with COPD [41]. Depression has been notably associated with reduced exercise tolerance [46, 49] and the degree of airflow limitation in patients with COPD [132].

In the general population, the presentation of diurnal variation in measures of positive and negative affect has been described as a defining feature of depression [125]. Moreover, Morris et al. [124] have demonstrated that individuals who report greater diurnal variation in their depressive symptoms suffer from more severe depression. Thus, depressive symptoms variability might be of use in patients with COPD to estimate the depression severity, and to our knowledge has yet to be investigated in clinical populations.

Evaluation of diurnal variation in depressive symptoms requires instruments that are easy to use, preferably short, quick, and repeatable using an ecological momentary assessment (EMA) method [128]. Previous studies conducted in patients suffering from depression have relied on the measurement of mood states (positive and negative affect) or on depression questionnaires not originally designed for use within an EMA context. Recently, Moullec et al. [127] developed and validated a short form of the Center for Epidemiologic Studies - Depression scale (CES-D)

specifically designed for EMA methodology. No published study, to our knowledge, has used such an instrument in COPD patients to gain a better understanding of the relationship between depression severity and the diurnal variation in the course of depressive symptoms. Yet, characterization of such patterns may be useful to design interventions with tailored content and timing in patients with severe comorbid depression.

The main objective of this pilot study was to investigate whether depression severity was associated with diurnal variation in depressive symptoms in COPD patients. Moreover, we examined this relationship within sub-types of depressive symptoms. Finally, we verified whether functional limitations mediated the relationship between severity of depression and diurnal variations of depressive symptoms in COPD patients.

METHODS

This pilot study was conducted as part of a larger project designed to evaluate the impact of time-of-day on the acute response to incremental exercise in COPD patients [173]. Participants were prospectively recruited from l'Hôpital du Sacré-Coeur de Montréal between August 2010 and April 2011 and were followed for the duration of one week. The institutional ethics committee approved the study procedure and signed informed consent was obtained from each participant. Eligibility criteria included: 1) being ≥ 40 years of age; 2) a smoking history ≥ 10 American pack-years (20 cigarettes/pack); 3) a post-bronchodilation forced expiratory volume in one second (FEV_1) < 80% of the predicted normal value; and 4) a FEV_1 to forced vital capacity (FVC) ratio < 0.7. Patients were excluded if: 1) they had a respiratory exacerbation (change in dyspnea or volume/color of sputum, need for antibiotic treatment, or need for hospitalization) within the past four weeks prior to the first hospital visit and therefore did not have clinically stable COPD; 2) active condition other than COPD (unstable coronary artery disease, severe arthritis, etc.); and 3) prescribed oxygen therapy. Consenting eligible participants completed initial assessments of pulmonary function, anthropometric measures, and depressive symptomatology on site. During the following week, depressive symptoms were assessed daily at home at three time points: morning, afternoon, and evening. During the data collection period, participants returned to the hospital for pulmonary function assessments and incremental exercise tests and the correct completion of the questionnaire were then verified.

Functional limitation of COPD patients was evaluated by standard spirometry, which measures the degree of respiratory impairment (i.e., measuring FEV_1, FEV_1/FVC ratio) [19], and by incremental cycling exercise test which measures the maximal exercise capacity of patients (i.e., peak work rate) [24]. These measures of functional limitation are strongly correlated with levels of everyday physical activity [196-198].

Additionally, the French validated version of the 20-item CES-D [140] was administered, between 10 am and 2 pm, to evaluate the severity of depressive symptoms. Respondents rated the frequency with which they experienced depressive symptoms in the past week on a four-point Likert scale ranging from 0 to 3. Scores can range from 0 to a maximum of 60, where a larger score represents a greater overall severity of depressive symptomatology.

For the one-week follow-up, each participant had a printed diary and completed the very short version of the CES-D (VS-CES-D) [127] three times daily over seven consecutive days. The VS-CES-D is a 4-item version of the CES-D, developed following recent recommendations for the development of short form tests [199]. It has excellent psychometric properties [127] and is specifically designed for EMA protocols. The dimensions of depressive symptomatology included positive affect ("I am happy"), depressed affect ("I have crying spells or feel like it"), disturbed interpersonal relationships ("I feel that people dislike me") and somatic complaints ("I talk less than usual"). Participants indicated how they felt at the present moment by drawing a vertical intersecting line on a 100-mm visual analog scale (VAS), with the descriptive terms "not at all" and "absolutely" on opposite ends. A fifth VAS asking to identify the midpoint on the 100-mm line was used as an "error measure". Each time of day was featured on a separate page and the four items were presented in a random order for each page and for different days. Participants were excluded in the case of three consecutive missing measures.

Data Analyses

The distribution of normality was verified using a normality plot (Q-Q plot). For each subject, the difference between the minimum and maximum scores on each VS-CES-D dimension was calculated for each day and averaged over the seven consecutive monitoring days. Depending on normality, Pearson or Spearman's rank correlations were then used to **test** the relationship between the continuous severity score of depression (CES-D) and the average

amplitude of diurnal change (Δmax-min) in each of the four dimensions of the VS-CES-D. Moreover, after having verified the relationships between functional limitation parameters and both depression severity and variability of depressive symptoms with bivariate analyses, we ran a series of linear regression models with functional parameters as covariates to explore their potential confounding role in our relationship of interest. All analyses were conducted using SPSS version 19 (Chicago, IL). Two-tailed p values at 0.05 were considered statistically significant.

RESULTS

Fourteen participants were recruited; one was excluded for having ≥ 3 consecutive missing measures at the VS-CES-D. Their clinical and socio-demographic characteristics are presented in Table 10. All participants were Caucasian and had been diagnosed with moderate to severe COPD [175] in the past 5 ± 3 years. Most of them were men (9/13) and retired (10/13).

The mean depression severity score measured with the CES-D questionnaire was of 12 ± 10. The mean diurnal variability (amplitude) of depressive symptoms were as follows: positive affect = 9.2 ± 9.7; depressed affect = 5.3 ± 7.5; somatic complaints = 6.6 ± 6.0, and disturbed interpersonal relationships = 5.4 ± 5.7.

The correlational analyses showed that higher CES-D scores were strongly associated with larger amplitude of diurnal change in depressive symptoms. Therefore, as depression severity got worst, the range in symptom responses throughout the day also became larger. As shown in Figure 8, positive affect ($r = 0.61$, $p = 0.02$); depressed affect ($r = 0.67$, $p = 0.01$); somatic complaints ($r = 0.82$, $p = 0.001$) and disturbed interpersonal relationships ($r = 0.71$, $p = 0.01$).

The results, as shown in Table 11, indicate that no significant correlations were found between functional limitation parameters and both depression severity or mean amplitude of diurnal change in depressive symptoms. These results were confirmed by our series of regression models including functional parameters as key covariates (results not shown -- available upon request to corresponding author) (see Appendix D).

DISCUSSION

To our knowledge, this is the first study to investigate diurnal variation in depressive symptoms in COPD patients. Our findings reveal that individuals with more severe depression symptoms have greater diurnal variability in all four depressive symptoms measured by the VS-CES-D. Furthermore, this greater diurnal variability in psychological distress appears to be independent of functional limitations of patients, suggesting that these momentary fluctuations may be specific to the severity of depression and not to the severity of COPD. Ecological momentary assessment of psychological distress should be considered in clinical nursing practice, notably at the start of a pulmonary rehabilitation (PR) program, to identify COPD patients with more severe comorbid depression and possibly determine the appropriate timing of specific interventions. Indeed, PR program appears to be an opportune time to evaluate for depression severity using such a brief tool, as health professionals are in repeated contact with COPD patients over a period of time typically lasting weeks or months. Depression is known to be associated with non-completion of PR [200, 201]. Such EMA approach may then bring new time-related information in order to optimize the compliance and adherence of these vulnerable participants to PR activity sessions.

The present study extends our knowledge on diurnal variation of depressive symptoms in individuals suffering from depression. This is the first study that used a very short depression questionnaire specifically designed for EMA context and with a multidimensional assessment of depressive symptoms. Interestingly, the somatic complaint dimension of the VS-CES-D (i.e., “I talk less than usual”) had the strongest relationship with severity of depression. A slower cadence, longer onset, and longer pauses in conversation is well known as a good marker of depression [202]. The present findings go further and suggest that a larger diurnal variation in this symptom would characterize a more severe depression.

The presence of comorbid depression complicates the management of COPD patients and has a negative impact on progression of COPD [50]. It would be interesting to evaluate if greater diurnal variation in depressive symptoms is a stronger predictor of COPD-related exacerbation than solely the diagnosis of depression. Moreover, further research might explore the interest of disease management interventions with tailored content and timing (e.g., telemonitoring

interventions with mobile phone SMS, pulmonary rehabilitation), to maintain healthy behavior in these COPD patients with greater diurnal variations in depressive symptoms.

Due to a certain number of limitations, the current results must be, however, interpreted with caution. First, the baseline CES-D questionnaire was not systematically administered at the same time. However, the CES-D was completed around the same range of time (10 am to 2 pm) reducing the risk of time-of-day effect. Additionally, given that a paper medium was used for the VS-CES-D, we could not verify the exact moment when the questionnaire was completed. However, completion of the journal was verified on days of participants' three visits at the research center [173], and participants were asked to report the time at which they completed the journal. Excellent adherence was then observed. Furthermore, as COPD patients are known for having an increased risk of cognitive impairments [203], the paper-and-pencil option seemed more appropriate than an electronic device in this population. The possible learning effect was limited by the randomization of the questions' order for each time of day and for each day. The major strength of using the VS-CES-D lies with its specific design for EMA and its measure of the multidimensionality of depression.

CONCLUSION

Depression comorbidity is a major concern in COPD by worsening its prognosis and interfering with effective COPD management. However, the identification of depression and its severity in patients with COPD remains problematic due to the overlap between physical symptoms of both disorders. The present proof-of-concept study suggests that greater diurnal variations in measures of psychological distress may be a relevant marker of more severe depression, independent of COPD severity. Brief and engaging questionnaires, as the VS-CES-D, may prove to be useful clinical tools to help characterise the severity of clinical depression in COPD patients. For future generations of patients to come, more at ease with electronic device, further research should definitely be undertaken to validate an electronic version of the VS-CES-D. Moreover, the present study should be repeated in larger prospective studies to determine whether greater diurnal mood variation increases the risk of worst outcomes in COPD, and worst response to treatment. EMA approach is uniquely well suited to capture depressive symptoms,

which are often transitory and not easily observable, and may guide researchers and clinicians to develop specific interventions with content and timing adjustments in COPD patients.

Table 10 - Demographics and Baseline Measurements

Sex (male/female)	9/4
Smoking status (current/former)	2/11
Smoking pack-years	45 ± 17
Age (yrs)	71 ± 7
BMI ($kg \cdot m^{-2}$)	27 ± 4
FEV_1 (L)	1.4 ± 0.4
FEV_1 (% pred.)	57 ± 13
FEV_1/FVC (%)	51 ± 9
Peak capacity (watt)	73 ± 17
CES-D score	11.9 ± 10.1

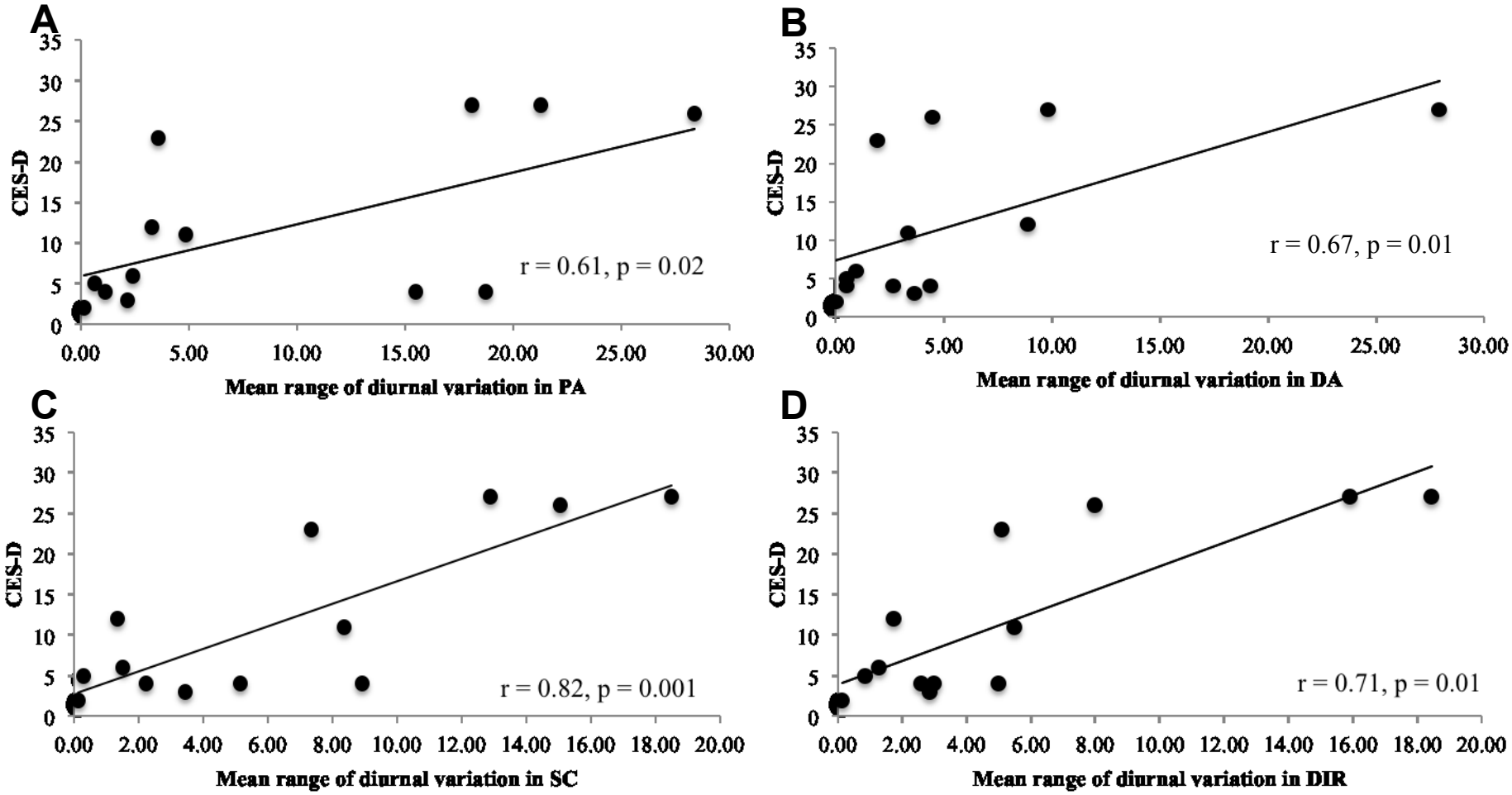
Mean ± SD unless otherwise specified

Table 11 Associations between functional limitations of COPD and both depression symptoms severity and diurnal variations of the four dimensions of depressive symptomatology

	CES-D total scores	Mean amplitude of diurnal variation – VS-CES-D			
		PA	DA	SC	DIR
FEV1 (L)	r = .10; p = 75	r = .15; p = .63	r = -.15; p = .62	r = .13; p = .68	r = .00; p = .99
FEV1 (% Pred)	r = -.04; p = .90	r = -.26; p = .38	r = -.20; p = .52	r = -.18; p = .57	r = -.12; p = .69
FEV1/FVC (%)	r = -.10; p = .75	r = .05; p = .86	r = .05; p = .88	r = .00; p = 1.00	r = -.08; p = .79
Peak work rate (W)	r = -.16; p = .60	r = -.18; p = .55	r = -.48; p = .09	r = -.32; p = .29	r = -.40; p = .17

Notes: Center for Epidemiologic Studies Depression scale (CES-D), Positive Affect (PA), Depressed Affect (DA), Somatic Complaints (SC), Disturbed Interpersonal Relationships (DIR), the forced expiratory volume in one second in liters and percentage of predicted (FEV_1), ratio between the FEV_1 and forced vital capacity [FVC], peak work rate in watts

Figure 8 **Average amplitude of diurnal variability in the four dimensions of depressive symptomatology in relation to baseline score on the Center for Epidemiological Studies Depression Scale (CES-D) in 13 COPD patients.**



Notes : 1A: Positive affect (PA); 1B: Depressed affect (DA); 1C: Somatic complaints (SC); 1D: Disturbed interpersonal relationships (DIR)

5.0 DISCUSSION

The main purpose of this thesis was to investigate diurnal variations in clinical measures (exercise capacity, pulmonary function and symptoms, psychological distress, and measures of the rest-activity cycle) in a COPD population and to explore the implications of these variations in the clinical assessment of COPD.

We first aimed to investigate the effect of time of day on exercise response, resting pulmonary function, and symptoms in COPD [173]. Overall, no statistically significant effect of time of day was detected on these measures in a convenience sample of 14 patients. However, when comparing exercise capacity at different times of day, the effect size was large (*f = 0.48)* [149]. Furthermore, when considering the clinical significance of time of day variations in these measures (i.e. suggested minimal clinical important difference (MCID) of 100ml for FEV_1, 150 ml for FVC, and 10 W for exercise capacity), a majority of the participants demonstrated significant changes in pulmonary function and exercise capacity [173]. The subgroup demonstrating greater diurnal variability in pulmonary function and exercise capacity where labeled as "varriers" and the unchanged subgroup as "non-varriers". Among the varriers, peak exercise capacity increased from the morning to the afternoon and was greatest at 16:00 hours [173], similar to the timing of peak exercise performance previously documented in healthy individuals [95, 96, 163]. Based on these findings, we advised that the recommendation to use a standardized time of day for repeated exercise testing be maintained in patients with COPD.

Next, we investigated the relationship between a clinical measure of circadian rhythms, using the rest-activity cycle, and indexes of disease severity and prognosis in COPD patients [204]. The circadian amplitude of the rest-activity cycle – or relative amplitude (RA) – was categorized as high or low using a median split approach, given the absence of normative values for this measure. A secondary objective was to compare the 24-hour activity profiles and sleep quality between high and low amplitude subgroups. Our results showed that individuals in the low RA subgroup had worse dyspnea and prognostic outcome (BODE+COTE), while those in the high RA subgroup had greater levels of physical activity between 12:00 and 15:00 hours [204]. Low RA as an indicator of greater disease severity and worse prognosis was consistent with the findings reported in other disease conditions [116-118, 131]. The difference in amplitude appears to be due to the increased physical activity in the afternoon in the high amplitude

subgroup. Increasing physical activity may be a target to improve RA using exercise-based rehabilitation programs in COPD.

The third objective was to investigate diurnal variations in depressive symptoms and their relationship with severity of psychological distress [174]. We found greater variations in positive and depressed affects, somatic complaints, and disturbed interpersonal relationships to be associated with increased severity of depression in COPD. Greater diurnal variability in depressive symptoms was not correlated with pulmonary function or exercise capacity, suggesting that the source of the variation may be specific to depression severity, and not to the severity of COPD. Given the difficulty in identifying depression in COPD, the measure of diurnal variability in depressive symptoms may be a useful clinical marker to identify severe depression.

5.1 Diurnal versus circadian variations

Observed variations in physiological and psychological variables typically result from the combined influence of the endogenous circadian rhythm and exogenous influences. Exogenous cues can include certain environmental and behavioural factors which may influence circadian rhythms such as light exposure, timing of dietary intake, social interaction, activity levels, and characteristics of the sleep-wake cycle [61].

Whether the diurnal variations in exercise capacity, rest-activity cycle, and symptoms of depression were due to an underlying endogenous circadian cycle or mostly the result of exogenous influences was not directly investigated. To determine whether a circadian component may have a role in the variation in the measures of exercise capacity and mood, they need to be compared with a marker of circadian rhythmicity such as melatonin [205, 206] or core body temperature [94, 207]. Core body temperature has demonstrated a sinusoidal rhythm with temperature peaking in the afternoon and its minimum occurring at night [94, 207]. In the literature, the afternoon peak in temperature has been shown to coincide with measures of peak aerobic capacity [93, 97, 100, 208], while the temperature minimum coincides with mood's lowest point in healthy individuals [121]. Therefore, the association of the measures related to exercise and mood with core body temperature seems to support the notion of a circadian component in their variation. Our results, in the varrier subgroup seems to follow the same pattern in peak

exercise capacity and may be due to a stronger, or better entrained circadian rhythm than in the non-varrier subgroup. A pattern of morning worsening in positive affect can be found in our participants with clinically significant depressive symptomology (CES-D >19). These findings are in line with the pattern that has been reported in depressed individuals [121, 122]. As for the rest-activity cycle, it is considered to be an accepted method of assessing circadian rhythms [209]. In a sample of middle-aged schizophrenia patients, melatonin production was compared between patients with high and low RA of the rest-activity cycle [113]. The authors observed an abnormal timing of the episode of melatonin secretion in the group with low amplitude, which may reflect a desynchronisation of circadian rhythms [69]. Moreover, in some patients with low RA, melatonin secretion was so low that it was not possible to determine the timing of the onset of secretion. We did not find supporting evidence of a phase shift in timing in our sleep parameters. The only indication of desynchronization of the circadian rhythm was the reduced amplitude found in a subgroup of individuals. Masubuchi et al. [210] investigated an individual with non-24-hour sleep-wake syndrome, where the circadian rhythm is desynchronized from both day-night and the sleep-wake cycle. Melatonin was administered to synchronize the circadian rhythm and compared with the desynchronized rhythm. When melatonin rhythms were phase matched, the desynchronized rhythm demonstrated reduced circadian amplitude. It is therefore possible that a low RA reflects an internal desynchronization of circadian rhythms and/or a general flattening of the endogenous circadian amplitude.

Our study design included four hospital visits and three evaluations at different times of day. These visits alone may have changed participants' daily amount of social interaction, their activity levels (leaving their domicile and travelling to the hospital), their light exposure (going outdoors to access the hospital), their wake time (for early morning evaluations), and their dietary intake (in prevision of evaluations). Conditions that were under our control, such as the environment within the laboratory, were precisely regulated during pulmonary function and exercise evaluations. Other factors that could impact behaviour may depend on personal motivation, effort during the evaluations and compliance with the assessments [24]. Activity level may also be influenced by behaviour and as a marker of circadian rhythms its response may be susceptible to masking influences. The actigraphic measures and mood assessments were collected under everyday conditions. Recruitment took place over an eight-month period and differences in the amount of light exposure and temperature range during that period may have

influenced changes in circadian rhythm. During winter, light exposure becomes reduced with shorter days [211]. Colder outdoor temperature may also lead to decreased levels of activity [212]. To control for some of these exogenous influences the study could have asked participants to stay in the lab throughout the study under controlled laboratory conditions (ie. light, temperature, humidity etc.). However, due to the nature of the study design, changes in dietary intake and sleep-wake cycle would remain unavoidable. These changes would be true to life situations when performing exercise at different times of day.

5.2 Diurnal variations and clinical outcome measures of COPD

5.2.1 Diurnal variation and respiratory function

Over a 24-hour period, it has been observed that FEV_1 may differ by as much as 286 ml in a stable COPD condition [75]. An increase of 100 ml in FEV_1 is often the target set for measuring improvement by bronchodilation in pharmacological clinical trials and this change is considered as clinically significant [135]. In our study, the change in expiratory airflow was not found to be statistically different during clinical hours, between 8:00 and 16:00 hours. However, we found a diurnal variability in FEV_1 that exceeded 100 ml in a majority of participants [173]. From the medical practitioner and patient's perspective, the clinical rather than statistical significance of changes in expiratory airflow may be of greater importance [213]. A change in FEV_1 of 100 ml is perceptible by COPD patients and can be treated with bronchodilator therapy [135]. Determining the circadian timing of pulmonary function is an opportunity to improve the management of COPD in clinical care.

An association between low amplitude of multiple rhythms, including cortisol, rest-activity, and blood pressure, have been reported with worse disease severity and prognosis in other disease conditions [116-118, 131]. In COPD, the measure of FEV_1 is used to characterize disease severity and treatment outcome, and has been shown to predict survival outcome [4]. We compared FEV_1 between patients with high versus low amplitude of the rest-activity cycle, and found no significant difference between the subgroups [204]. We also investigated the relationship between respiratory function (FEV_1, FEV_1/FVC) and measures of depression. No significant correlation was found between respiratory function and the amplitude of variation in depression symptoms, or between respiratory function and depression symptom severity [174].

However, the effects of COPD extend beyond the lungs and include extra pulmonary systems [214]. Therefore, other measures are necessary in the assessment of COPD [215]. Other independent outcome measures also shown to predict survival outcome in COPD include body mass index (BMI), respiratory symptoms, and exercise capacity [215]. Composite measures that combine these outcomes and measures of comorbidities produce stronger predictors than FEV_1 alone [39, 59, 216]. When composite measures were compared between patients with high and low amplitude of the rest-activity cycle, differences were found in favor of the high amplitude subgroup [204]. This suggests that amplitude of the rest-activity cycle may be a marker of global prognosis.

5.2.2 Diurnal variation and COPD symptoms

The morning worsening of symptoms has been demonstrated in severe COPD [83-85]. In our study, we did not find significant variations in resting or exercising dyspnea at different times of day when dyspnea was evaluated using the Borg scale [173]. We may not have found the same pattern because only two participants had severe disease severity; the majority of our sample had moderate disease severity. Additionally, the Borg scale uses a discrete assessment of dyspnea, every minute during exercise, and may be limited by maximal exercise tests of shorter durations [217]. During exercise, a continuous assessment of dyspnea has been proposed as it increases the accuracy of capturing the changes in dyspnea [218]. We also compared the high and low RA of the rest-activity cycle with the severity of dyspnea under everyday conditions using the mMRC dyspnea scale and found greater severity in dyspnea in the low amplitude of the rest-activity cycle subgroup [204]. In a study by Kessler et al. [83] greater variability of respiratory symptoms over the period of the day has been associated with more severe dyspnea and greater limitation to exercise. Based on this information, it could be hypothesized that greater variability in respiratory symptoms may also be associated with a reduced circadian amplitude. Variability in respiratory symptoms may be due to diurnal changes in airway caliber, or due to changes in behavioral factors like physical activity or a sign of poor control in COPD management such as pharmacological therapy [83, 84]. Future studies are needed to determine the role of symptom variability and the influence of the endogenous rhythm. Additionally, it would need to be verified if treatments that improved symptoms and possibly the underlying circadian rhythm could improve prognosis outcome [9, 76, 219].

5.2.3 Diurnal variation and amplitude of the rest-activity cycle

Based on our findings, we observed that the subgroup of individuals who demonstrated clinically significant variability in pulmonary function and exercise capacity (the "varriers") had a pattern of diurnal variations that did not appear to be random [173]. The varrier group demonstrated a peak in response in exercise capacity in the afternoon, similar to what had been reported with studies investigating circadian variation in aerobic capacity [93, 97, 100, 208]. We had hypothesized that the varriers may have a larger circadian amplitude, which may indicate better internal synchronization with physiological function [71, 173]. Therefore, we verified whether the varriers where also the patients with the larger amplitude of the rest-activity cycle. We found that only six individuals fell in the same category with both approaches; three indicated better underlying circadian rhythm by being varriers with a high relative amplitude, and three indicated worse underlying circadian rhythm by being non-varriers with a low relative amplitude. The remaining eight were equally divided between varriers with low amplitude, and non-varriers with high amplitude. No clear relationship between the varriers and amplitude subgroups could therefore be drawn. Individually, the measures of respiratory function and exercise capacity did not have a significant association with amplitude of the rest-activity cycle ($p = 0.97$ for FEV_1%predicted, and $p = 0.24$ for VO_{2peak}%predicted). Since the literature supports the measure of amplitude of the rest-activity cycle as an indicator of underlying circadian rhythmicity [209, 220, 221], the diurnal variability in the varriers may not reflect internal circadian characteristics. The varrier subgroup had a significantly greater BMI than the non-varrier subgroup, which may indicate better-preserved muscular function and be an indicator of better prognosis outcome [160-162]. However, no significant difference was found when comparing high and low amplitude of the rest-activity cycle with BMI [204]. Therefore, muscular function may be a contributing factor to the varrier subgroup. However, even with the ability to attain greater exercise capacity in the afternoon in the varrier subgroup, it seems the strength of the circadian amplitude may be a factor that contributes to increased levels of voluntary activity in the afternoon. If we were able to improve both muscular function and amplitude, this may lead to optimal outcomes.

A negative association between circadian rhythms and depression severity has been reported in the literature. The amplitude of body temperature [182], melatonin [222] and rest-

activity cycle [184] have been found to be reduced in more severe depression. This suggests a possible desynchronization of the endogenous circadian rhythm in depression [123]. However, in our study we did not find an association between increased depression scores and lower amplitude of the rest-activity cycle [204]. Therefore, other factors may contribute to increased depression severity such as female sex [223], or lack of social support [44, 224, 225]. It does not seem like sex played a role in our results as no significant difference was found when sex was compared between high and low amplitude of the rest-activity cycle. We cannot comment on their level of social support, as we did not collect information on the participant's social network. Medication is a factor that could improve depression symptom severity and may play a confounding role. Two individuals, who were part of the low amplitude group, were prescribed anti-depressive medication and had lower depression scores. The low depression scores may have influenced the low amplitude group mean score and may be a reason why no significant difference was found when compared to the high amplitude group. This means that the anti-depressive medication may have reduced depression severity but did not resolve the desynchronization of the circadian rhythm. Other methods of improving depression severity and circadian rhythm need to be explored.

Lower circadian amplitude has been associated with greater diurnal variation in mood [226]. Therefore, we used our measure of diurnal variation in depressive symptoms and compared it between the high and low amplitude groups. Diurnal variation in depressive symptoms was greater in the low amplitude group in three out of the four of the depressive symptoms. However, positive affect was the only symptom for which the difference was significant. It is possible that depending on the depressive symptom, diurnal changes may be more or less perceptible. We also investigated the relationship between diurnal variations in depressive symptoms and depression severity. We found that greater diurnal variation in depressive symptoms was related to greater depression severity [174]. Therefore, the measure of increased diurnal variability in depressive symptoms may be a useful marker in relation to identifying lower RA and increased depression severity.

5.3 Implications for the management of COPD

Our results suggest that diurnal variability may be an important factor in the assessment and follow-up of COPD patients. Accounting for diurnal variation by standardizing time of day for repeated assessments of pulmonary function and exercise capacity would help limit variability and permit better interpretability of outcomes in research and clinical practice. The assessment of circadian amplitude or diurnal variation in depressive symptoms may also prove useful in the interpretation of dyspnea and depression severity, and prognosis outcomes.

In the first series of analyses, we investigated how different timings of exercise could affect performance in COPD. We found a subset of individuals with COPD who were varriers, with amplitudes of change exceeding the minimal clinical important difference for pulmonary function and exercise capacity. The varriers had an exercise capacity that peaked at 16:00 hours [173]. Whether or not varrier status may be able to predict other clinical outcomes has yet to be investigated. However, the significance of a peak in exercise capacity in the afternoon in a subgroup of individuals may still be clinically important. This information could be used to schedule pulmonary rehabilitation sessions. As the timing in peak exercise capacity aligns with circadian changes in body temperature [92, 94], further increasing exercise output in synchronization with the endogenous cycle may be able to improve circadian amplitude rhythm.

In the second series of analyses, we compared the amplitude of the rest-activity cycle to the 24-hour activity levels and it was found that the high amplitude group had greater activity levels in the afternoon as compared to the low amplitude group [204]. Respiratory symptoms have been documented to be worse in the morning, where simply performing activities of daily living can be a struggle in some individuals with COPD [227, 228]. Therefore, symptoms may be a limiting factor to physical activity and may influence adaptive behaviours such as being more active later in the day. The findings on peak exercise capacity, increased levels of physical activity and respiratory symptoms seem to favor increasing activity in the afternoon. While the present thesis did not directly investigate treatment strategies, such as pulmonary rehabilitation training, our results and those reported in the literature may be relevant in helping to determine when would be a more optimal time to perform aerobic exercise. Generally, an increased training intensity leads to greater adaptations from exercise and leads to increased exercise capacity [229]. To date, different methods have been investigated to try and achieve an increase in training

stimulus in individuals with COPD, such as supplementary oxygen or heliox during exercise [229], or using different training protocols such as one-legged cycling [230]. In order to boost exercise training intensity and achieve greater gains in exercise capacity, exercise could be aimed at a more propitious time to take advantage of naturally occurring diurnal changes.

In the third series of analyses, our findings were consistent with Morris et al. [124] who found a greater variability in depressive symptoms to be associated with more severe depression symptoms. Our study was the first to demonstrate this in a COPD population. This is significant as the overlap between symptoms of COPD and those of depression can mask the severity of depression in COPD patients [174]. The Ecological Momentary Assessment (EMA) approach could be used in the follow up of patients as well as for the early detection of depressive disorders requiring intervention. There are no standard guidelines for using EMA, although questionnaires should be brief and clear so they can be repeated multiple times in a day [128]. We used at least three moments during the day to obtain significant diurnal variation in depressive symptoms over the period of at least a week. Participants could be asked to complete the VS-CES-D when they subjectively feel their mood is at its best and worst during the day to determine the full range in diurnal variation. We used a paper medium, however an electronic device could be used to confirm the timing of recordings. Assessing the presence of diurnal variation in depressive symptoms may be useful in clinical practice to detect concomitant depression.

Investigating time-of-day variations in exercise response was an important concept in this thesis. It has been hypothesized that exercise may be a non-photic synchronizer of circadian rhythmicity [231, 232]. The study of exercise as a synchronizer may be useful in COPD as part of its management and treatment. Identifying the time of day when exercise may be optimal, for the synchronization of circadian timing, has yet to be determined. Rubio-Sastre et al. [231] were the first to investigate timing of exercise in healthy women and its effect on the circadian rhythm amplitude and acrophase, via circadian wrist temperature assessment. They found that exercise in the evening, running for 45 minutes at 21:00 hours, resulted in a reduced amplitude of the temperature rhythm when compared to a control week without exercise. Therefore, exercising in the evening may actually impair the circadian rhythm [231]. In individuals at increased risk for worse health outcome, exercising may be better suited at other times of day. No significant

difference was found with exercising in the morning (9:00 hours). Evening exercise also resulted in approximately 2-hour phase delays [231]. Exercising in the evening may be able to assist in the re-entrainment of circadian rhythms, which require a delay in the rest-activity cycle [233]. In COPD, the timing of exercise would also need to account for physiologic and symptomatic changes, which may favor exercise in the afternoon. In the future, strategies to increase circadian amplitude may be a useful therapeutic target. Particularly, increasing physical activity may improve respiratory and depressive symptoms and prognosis outcomes in COPD. In the literature it has been shown that increased depression severity was associated with worse exercise capacity [46]. Moreover, improving exercise capacity was shown to reduce depressive symptoms [234]. Here again exercise may act as a synchronizer in maintaining an active daily lifestyle, which may help to normalize diurnal variation in depressive symptoms and perhaps reduce depression severity.

5.4 Strengths and limitations

The body of work for my thesis originates from a research protocol, which was designed to answer the question of whether time of day had an effect on peak exercise capacity in individuals with COPD. In addition to exercise evaluations and pulmonary function, a very diverse dataset was prospectively collected including actigraghy data and psychological distress measures, thus permitting the postulation of supplementary scientific questions and a second and third series of analyses. The protocol was conducted using the highest methodological standards for laboratory evaluations (equipment calibrations and standardization of procedures), for actigraphy (data collected together with a journal to discriminate bedtime, wake times, and watch removal) and for the assessment of psychological distress (EMA approach, which minimizes recall bias). However, certain methodological limitations in the design of the second and third series of analyses need to be addressed. Retrospectively, different methods could have been selected. Ideally, a biological marker, such as melatonin or cortisol, could have been included to assess circadian rhythmicity. Additionally, including a formal clinical interview to determine the diagnosis of psychological distress would have been the optimal choice [42]. Yet, changing the methodology could also have an impact on the overall study design, as assessments would have been lengthier and more complex.

The statistical analysis selected for the second series of analyses was based on methodology previously used by Bromundt et al.[113]. A median-split was used to dichotomize relative amplitude into high and low categories. Such an approach can reduce the statistical power, however our findings did not suggest that this was an issue in our study; also, since the means were compared, we lost discriminatory information between individuals who had different values within the same group [235]. A further limitation to this method of analysis is that it uses an arbitrary cut-off value that may have no clinical meaning, thereby potentially introducing a bias in the interpretation of the results. Individuals with values around the median split may thus end up in opposite categories while, in reality, be very similar. As mentioned previously, this approach was used because there is no currently accepted "normal value" for RA of the rest-activity cycle. However, we did compare our median value with what had previously been reported in the literature and found close similarities [113, 179]. Our findings are also in line with findings in other diseases that have reported a relationship between various measures of circadian amplitude and disease severity and prognosis outcomes [116-118, 131].

The timing of assessments is likely to have an important role in the interpretation of the measures. The timing of evaluations for the pulmonary and exercise evaluations were selected based on clinical testing hours. If the aim was to identify the maximal differences in response, a larger range in time or a greater number of evaluations could have been used. The timing of mood was assessed in the morning, afternoon, and evening. Participants were asked to report the time that they completed the questionnaire, but since it used a paper medium, we cannot verify the exact moment when it was completed. A set time for the initial visit when assessing baseline mood with the CES-D questionnaire was not standardized, but as it was scheduled around the same range of time, between 10:00 and 14:00 hours, it should not have affected the results.

When recruiting participants in a protocol requiring repeated exercise testing, it is possible that a selection bias towards individuals who were in better condition than the average COPD population occurred. Participants were also asked to cease taking their respiratory medication for at least six hours before the exercise evaluations and this too may have had an influence on who decided to participate in the study. For example, individuals with worse respiratory symptoms or more anxiety related to the short cessation of their respiratory medications may have declined to participate. Furthermore, our eligibility criteria excluded

participants on oxygen therapy; therefore, our sample was mainly comprised of individuals with moderate disease severity. In future studies, assessing a larger sample would be necessary and would permit the evaluation of a greater number of confounders, such as variability in disease severity, exercise capacity, the influence of co-morbid diseases, etc.

5.5 Future Directions

Continuing from the first series of analyses, it would be of clinical interest to identify when ventilatory limitation, including subjective symptom perception, would be at its lowest and to identify the optimal timing for activity to elicit the greatest gains in exercise capacity. The diurnal variation in exercise capacity needs to be further studied to determine the most optimal time to perform physical activity. This would be an opportunity to work with patients' naturally occurring diurnal variations to optimize treatment and their outcome.

An endurance exercise test may be a better measure for evaluating exercise capacity as it has been shown to be more responsive to changes in treatment than the maximal exercise test [24, 148, 236]. An endurance exercise test may be performed at a constant load, a percentage of the maximal capacity, and endurance time is measured [24]. In addition to these measures, the history of previous exacerbations could be assessed as exacerbations have been shown to contribute to worse disease severity and decreased exercise capacity in COPD [1, 237]. Exacerbations can also contribute to increased day-to-day variability in respiratory symptoms [83].

The focus of this research was on diurnal variations in COPD measures. Novel outcome indicators were proposed, the rest-activity cycle as a potential indicator of disease severity and prognosis, and the variability in depressive symptoms to identify more severe depression. Further research is required in a larger scale study to confirm our conclusions. The objective in a future project would be to identify if exercise training could improve the circadian amplitude. The time of day exercise is performed has been shown to influence circadian rhythm measures [231]. The level of physical fitness can also influence amplitude changes as more fit individuals have more robust circadian rhythms [238]. Additionally, a combination of factors, such as training intensity, frequency and duration, and length of program may have an effect on outcome and will need to be evaluated to determine changes in amplitude and phase [239]. Van Someren et al. [179] were

able to demonstrate that a 3-month aerobic exercise training program, three times a week, with a duration of 1.5 hours, performed at noon, was beneficial in reducing the fragmentation of the diurnal rhythm. Further research would need to evaluate if there were an association with circadian amplitude and COPD severity, depression severity and prognosis outcome, pre and post exercise intervention. A biological marker, like melatonin, could be used to confirm circadian amplitude. A structured psychological interview could be used to determine depression cases and verify if the diurnal variation in depressive symptoms is a valid method of assisting in the identification of depression.

6.0 CONCLUSION

The body of work presented in my thesis was pilot work using the novel perspective of diurnal variations in COPD to investigate their effects on clinical assessments and outcomes. Altogether, these findings seem to indicate a clinically important role for the standardized timing of assessments in pulmonary function and exercise capacity and a possible role for the measures of relative amplitude of the rest-activity cycle and variability in depressive symptoms as novel outcome indicators. The difference in timing of evaluations may need to be accounted for and utilized in the timing of treatment management. Repeated exercise testing should be conducted at the same time of day to reduce variability and increase interpretability of response. Amplitude of the rest-activity cycle may be a useful indicator of COPD outcome, and low physical activity in the afternoon may be a target for improvement with pulmonary rehabilitation programs. Finally, identifying diurnal variation in depressive symptoms may be a novel way of identifying depression severity in COPD.

7.0 REFERENCES

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Appendix A – Participant Journal

Étude des variations diurnes de la tolérance à l'effort dans la maladie pulmonaire obstructive chronique

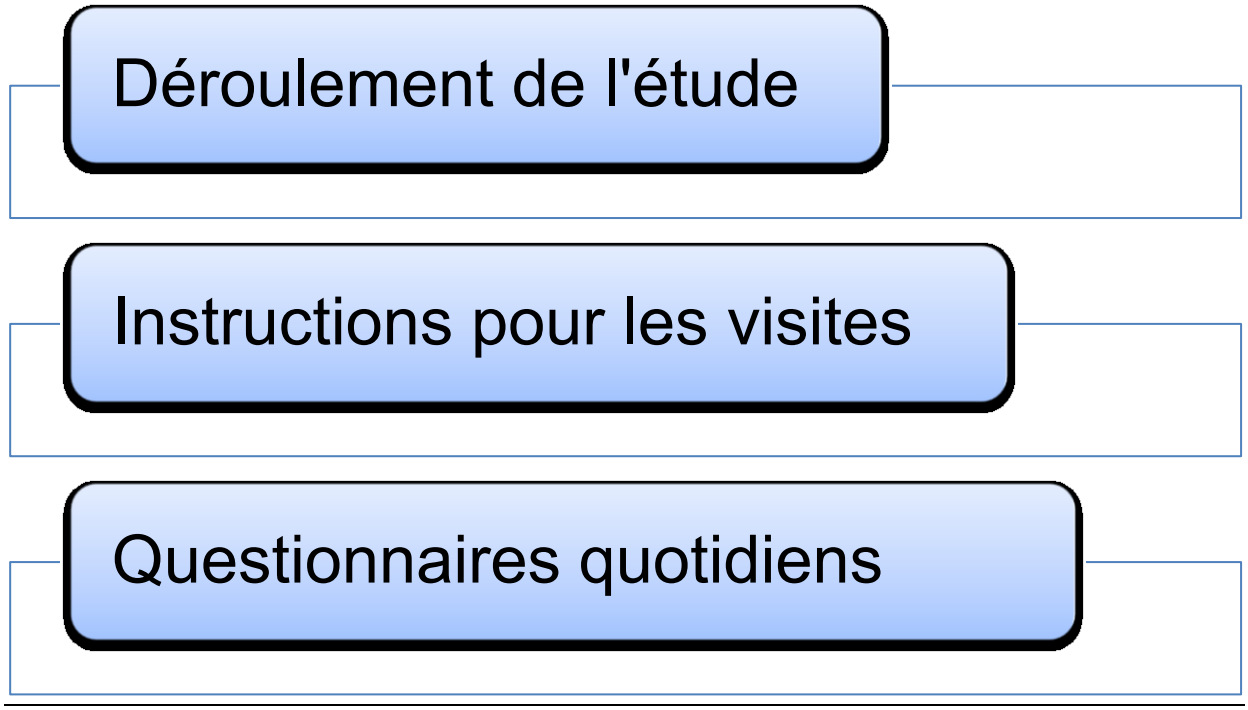
Carnet de suivi

Nom du participant: _____
Date départ: _____
Date de fin: _____

Personne de contact: **Emilie Chan-Thim**
Numéro: **514-338-2222 post 3944**

1er visite: _____ Hr: _____
2e visite: _____ Hr: _____
3e visite: _____ Hr: _____
4e visite: _____ Hr: _____

HÔPITAL DU SACRÉ-COEUR DE MONTRÉAL
HSCM


Déroulement de l'étude
Instructions pour les visites
Questionnaires quotidiens

Déroulement de l'étude

	1ère visite	Carnet de suivi	2ème, 3ème, et 4ème visite
Durée des visites:	1h30		chaque visite = 2h
Procédures:	Formulaire de consentement Questionnaire de chronotype Questionnaire d'humeur Évaluation des fonctions pulmonaires Familiarisation avec les épreuves d'effort Remise et explication du carnet de suivi	Journal alimentaire Prise des médicaments Questionnaire du matin, midi et soir Questionnaire d'humeur Actigraphie	Évaluation des fonctions pulmonaires Épreuve maximale sur vélo
Compensation:	un versement de $50 à la fin de la 4 ème visite du protocole		

Instructions pour les visites

À suivre avant chaque épreuve d'effort

1- Évitez de manger un repas copieux dans les 3 heures précédant l'épreuve d'effort. Limitez-vous à une collation.

2- Évitez de boire de l'alcool ou tout breuvage avec caféine (café, thé ou boisson gazeuse) 3 heures avant l'épreuve d'effort.

3- Évitez de fumer 3 heures avant l'épreuve d'effort.

4- Évitez de porter du vernis à l'ongle

5- Soyez reposé(e), évitez de faire de l'exercice le jour de l'épreuve d'effort.

6- Portez des vêtements souples et confortables et des chaussures de sport.

7- Il est possible que vous soyez fatigué(e) après l'évaluation; au besoin, prévoyez que quelqu'un vienne vous chercher et vous raccompagne à la maison.

8- Buvez beaucoup (préférablement de l'eau) dans les 24 heures précédant l'évaluation pour vous assurer d'être bien hydraté(e).

9- Si vous êtes diabétique, apportez votre glucomètre et une collation.

10- Apportez votre carnet de suivi à chaque visite du protocole.

11- Apportez vos médicaments "de secours".

12- Suivre les consignes pour le sevrage de vos médicaments.

Sevrage de médicaments avant chacune des visites

Visite 2 :

Date : _____

Médicaments	Ne pas prendre après

Visite 3 :

Date : _____

Médicaments	Ne pas prendre après

Visite 4 :

Date : _____

Médicaments	Ne pas prendre après

Consignes pour remplir le carnet

- Chaque jour, vous avez 3 questionnaires à remplir:
    1. Questionnaires du **matin**: à remplir après le déjeuner
    2. Questionnaires du **midi**: à remplir après le dîner
    3. Questionnaires du **soir**: à remplir après le souper

- Indiquez, en haut de la page, l'heure à laquelle vous remplissez chaque questionnaire.

- Le carnet doit être rempli pendant 7 journées consecutives du _____ au _____ inclusivement.

- Veuillez répondre à toutes les questions, il y a plusieurs parties à remplir :

    Matin :
    Description de l'alimentation
    Heures de la prise de médicaments
    Questions sur le sommeil (7 questions)
    Questionnaire sur l'humeur (6 questions)

    Midi :
    Description de l'alimentation
    Heures de la prise de médicaments
    Questionnaire sur l'humeur (6 questions)

    Soir :
    Description de l'alimentation
    Heures de la prise de médicaments
    Questions sur vos activités (3 questions)
    Questionnaire sur l'humeur (6 questions)

Si vous avez d'autres commentaires ou évènements spéciaux qui pourraient avoir influencé votre état dans la journée, vous pouvez les écrire en bas de la page des questionnaires du soir.

Consignes pour remplir le journal d'alimentation et la liste des médicaments

- Indiquez l'heure de vos repas et de vos collations.
- Donner une description complète de votre alimentation.
- Soyez le plus précis possible.

  Par exemple :
  Produits céréaliers,
  Légumes et fruits,
  Viandes ou substituts,
  Huiles et matières grasses,
  Lait ou substituts,
  Breuvages et produits caffeiné ou alcool,
  Autre

- Indiquez l'heure de la prise des médicaments ainsi qu'une liste de ces médicaments et leur dosage.
- Si vous fumez, indiquez les heures auxquelles vous avez fumé et le nombre de cigarettes (ou cigares et/ou pipes).

Exemple :

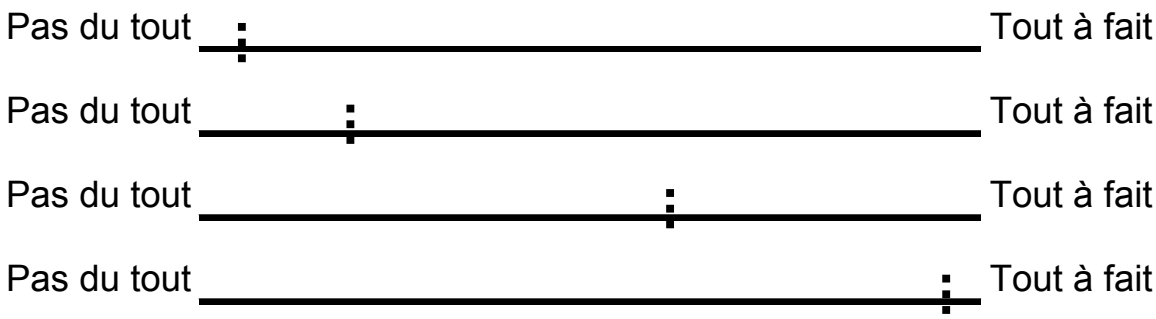
Heure:	Description d'alimentation
Déjeuner:	1 pain pita au blé entier, 1 petit morceau de fromage pour garnir
9h00	Demi tasse thé avec une demi tasse de lait 1%
Collation:	1 banane, 10 amandes sans sel
10h30	

Heure:	Liste de médicaments (dosage)
9h00	Advair (100mcg), Asaphen ec 80mg

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

Consignes pour remplir les questionnaires d'humeur

Durant la **semaine de suivi**, nous vous demandons de répondre 3 fois par jour à 5 questions qui correspondent à des sentiments que vous éprouvez sur vous-même. Pour chacune, nous vous demandons de faire **un trait vertical** entre les bornes « pas du tout » et « tout à fait » sur la ligne horizontale en fonction de l'intensité choisie. Il s'agit d'échelle visuelle analogique. Le principe de réponse à ces échelles vous est présenté ci-dessous. Ceci n'est qu'un exemple des multiples réponses possibles.



Aucune réponse n'est juste, elle est avant tout personnelle.

Instructions pour les sujets portant le moniteur Actiwatch

- Vous devez porter un moniteur au poignet _____ de façon continue (autant que possible), 24 heures par jour, incluant la période de sommeil.

- Si vous faites des activités durant lesquelles vous ne pouvez pas garder le moniteur (ex : bain/douche, laver la vaisselle, natation), écrivez dans votre agenda les heures durant lesquelles vous avez retiré le moniteur en indiquant la raison.

- **Les moniteurs sont résistants à l'eau, mais pas imperméables. Ne pas les plonger dans l'eau et veiller à les protéger autant que possible de la pluie.**

- Les moniteurs sont sensibles aux chocs : évitez autant que possible de les cogner ou de les échapper.

- Ne jamais essayer d'ouvrir les moniteurs ou de démonter une de leurs pièces.

- Veuillez indiquer avec le plus de précision possible vos heures de lever et de coucher dans les agendas de sommeil. Cette information nous aidera à interpréter vos données.

- Veuillez presser le marqueur sur l'actiwatch pour préciser quand vous fermer la lumière au coucher et la sortis du lit le matin.

Questionnaires quotidiens

Heure :_____ **Questionnaire du Matin 1**

Heure:	Description d'alimentation
Déjeuner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **A quelle heure vous êtes vous couché(e) hier soir?** ____h____
2. **Combien de temps avez-vous pris pour vous endormir?**
   ❑ moins de 15 minutes ❑ 15 à 30 minutes ❑ 30 à 60 minutes ❑ 1 heure ou plus
3. **Vous êtes-vous réveillé(e) durant la nuit?** ❑ Non ❑ Oui

Si oui, combien de fois ?__ Qu'est-ce qui vous a réveillé(e)?_____

4. **A quelle heure vous êtes-vous <u>réveillé(e)</u> pour de bon ce matin?** ____h____
5. **A quelle heure vous êtes-vous <u>levé(e)</u> ce matin ?** ____h____
6. **Sur une échelle de 1 (très mal dormi) à 5 (très bien dormi), entourez le chiffre correspondant le mieux à la qualité de votre sommeil:**

   1 2 3 4 5

   Très mal dormi Très bien dormi
7. **Sur une échelle de 1 (très fatigué(e), endormi(e), faible) à 5 (très en forme, éveillé(e), énergique), entourez le chiffre correspondant à votre forme au levé :**

   1 2 3 4 5

   Très fatigué(e) Très en forme

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis heureux(se)

Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots

Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas

Pas du tout _____ Tout à fait

Je parle moins que d'habitude

Pas du tout _____ Tout à fait

Je suis incapable de me détendre

Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ **Questionnaire du Midi 1**

Heure:	Description d'alimentation
Dîner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis heureux(se)
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ Questionnaire du Soir 1

Heure:	Description d'alimentation
Souper:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **Avez-vous fait une sieste aujourd'hui?** __ Non __ Oui
   Si oui, de quelle heure à quelle heure? De _____ à _____
   Avez-vous dormi? _____
2. **Avez-vous fait des activités physiques aujourd'hui?** __ Non __ Oui
   Si oui: Quoi et à quelle heure: _____
3. **Avez-vous enlevé le moniteur d'activité ?** __ Non __ Oui
   Si oui, de quelle heure à quelle heure? De _____ à _____
   Pourquoi ? _____

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Je suis heureux(se)
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

Veuillez mettre un trait au centre de la ligne ci-dessous

_____

Autres évènements de la journée à indiquer :

.....
.....
.....
.....
.....
.....

Heure :_____ Questionnaire du Matin 2

Heure:	Description d'alimentation
Déjeuner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **A quelle heure vous êtes vous couché(e) hier soir?** ____h____
2. **Combien de temps avez-vous pris pour vous endormir?**
   ❑ moins de 15 minutes ❑ 15 à 30 minutes ❑ 30 à 60 minutes ❑ 1 heure ou plus
3. **Vous êtes-vous réveillé(e) durant la nuit?** ❑ Non ❑ Oui
   Si oui, combien de fois ?__ Qu'est-ce qui vous a réveillé(e)?_____
4. **A quelle heure vous êtes-vous <u>réveillé(e)</u> pour de bon ce matin?** ____h____
5. **A quelle heure vous êtes-vous <u>levé(e)</u> ce matin ?** ____h____
6. **Sur une échelle de 1 (très mal dormi) à 5 (très bien dormi), entourez le chiffre correspondant le mieux à la qualité de votre sommeil:**

   1 2 3 4 5

   Très mal dormi Très bien dormi
7. **Sur une échelle de 1 (très fatigué(e), endormi(e), faible) à 5 (très en forme, éveillé(e), énergique), entourez le chiffre correspondent à votre forme au levé :**

   1 2 3 4 5

   Très fatigué(e) Très en forme

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis heureux(se)
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ **Questionnaire du Midi 2**

Heure:	Description d'alimentation
Dîner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Je suis heureux(se)
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ Questionnaire du Soir 2

Heure:	Description d'alimentation
Souper:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **Avez-vous fait une sieste aujourd'hui?** __ Non __ Oui

   Si oui, de quelle heure à quelle heure? De _____ à _____

   Avez-vous dormi? _____

2. **Avez-vous fait des activités physiques aujourd'hui?** __ Non __ Oui

   Si oui: Quoi et à quelle heure: _____

3. **Avez-vous enlevé le moniteur d'activité ?** __ Non __ Oui

   Si oui, de quelle heure à quelle heure? De _____ à _____

   Pourquoi ? _____

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots

Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas

Pas du tout _____ Tout à fait

Je parle moins que d'habitude

Pas du tout _____ Tout à fait

Je suis heureux(se)

Pas du tout _____ Tout à fait

Je suis incapable de me détendre

Pas du tout _____ Tout à fait

Veuillez mettre un trait au centre de la ligne ci-dessous

_____

Autres évènements de la journée à indiquer :

.....
.....
.....
.....
.....

Heure :_____ Questionnaire du Matin 3

Heure:	Description d'alimentation
Déjeuner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **A quelle heure vous êtes vous couché(e) hier soir?** ____h____
2. **Combien de temps avez-vous pris pour vous endormir?**
   ❑ moins de 15 minutes ❑ 15 à 30 minutes ❑ 30 à 60 minutes ❑ 1 heure ou plus
3. **Vous êtes-vous réveillé(e) durant la nuit?** ❑ Non ❑ Oui
   Si oui, combien de fois ?__ Qu'est-ce qui vous a réveillé(e)?_____
4. **A quelle heure vous êtes-vous <u>reveillé(e)</u> pour de bon ce matin?** ____h____
5. **A quelle heure vous êtes-vous <u>levé(e)</u> ce matin ?** ____h____
6. **Sur une échelle de 1 (très mal dormi) à 5 (très bien dormi), entourez le chiffre correspondant le mieux à la qualité de votre sommeil:**
   1 2 3 4 5
   Très mal dormi Très bien dormi
7. **Sur une échelle de 1 (très fatigué(e), endormi(e), faible) à 5 (très en forme, éveillé(e), énergique), entourez le chiffre correspondent à votre forme au levé :**
   1 2 3 4 5
   Très fatigué(e) Très en forme

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis heureux(se)
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ **Questionnaire du Midi 3**

Heure:	Description d'alimentation
Dîner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis heureux(se)

Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas

Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots

Pas du tout _____ Tout à fait

Je parle moins que d'habitude

Pas du tout _____ Tout à fait

Je suis incapable de me détendre

Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ Questionnaire du Soir 3

Heure:	Description d'alimentation
Souper:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **Avez-vous fait une sieste aujourd'hui?** __ Non __ Oui
   Si oui, de quelle heure à quelle heure? De _____ à _____
   Avez-vous dormi? _____
2. **Avez-vous fait des activités physiques aujourd'hui?** __ Non __ Oui
   Si oui: Quoi et à quelle heure: _____
3. **Avez-vous enlevé le moniteur d'activité ?** __ Non __ Oui
   Si oui, de quelle heure à quelle heure? De _____ à _____
   Pourquoi ? _____

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Je suis heureux(se)
Pas du tout _____ Tout à fait

Veuillez mettre un trait au centre de la ligne ci-dessous

_____

Autres évènements de la journée à indiquer :

.....
.....
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.....
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Heure :_____ Questionnaire du Matin 4

Heure:	Description d'alimentation
Déjeuner:	
Collation:	

Heure:	Liste de medicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **A quelle heure vous êtes vous couché(e) hier soir?** ____h____
2. **Combien de temps avez-vous pris pour vous endormir?**
   ❑ moins de 15 minutes ❑ 15 à 30 minutes ❑ 30 à 60 minutes ❑ 1 heure ou plus
3. **Vous êtes-vous réveillé(e) durant la nuit?** ❑ Non ❑ Oui
   Si oui, combien de fois ?__ Qu'est-ce qui vous a réveillé(e)?_____
4. **A quelle heure vous êtes-vous <u>reveillé(e)</u> pour de bon ce matin?** ____h____
5. **A quelle heure vous êtes-vous <u>levé(e)</u> ce matin ?** ____h____
6. **Sur une échelle de 1 (très mal dormi) à 5 (très bien dormi), entourez le chiffre correspondant le mieux à la qualité de votre sommeil:**
   1 2 3 4 5
   Très mal dormi Très bien dormi
7. **Sur une échelle de 1 (très fatigué(e), endormi(e), faible) à 5 (très en forme, éveillé(e), énergique), entourez le chiffre correspondent à votre forme au levé :**
   1 2 3 4 5
   Très fatigué(e) Très en forme

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Je suis heureux(se)
Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ **Questionnaire du Midi 4**

Heure:	Description d'alimentation
Dîner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis heureux(se)
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ Questionnaire du Soir 4

Heure:	Description d'alimentation
Souper:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **Avez-vous fait une sieste aujourd'hui?** __ Non __ Oui
   Si oui, de quelle heure à quelle heure? De _____ à _____
   Avez-vous dormi? _____
2. **Avez-vous fait des activités physiques aujourd'hui?** __ Non __ Oui
   Si oui: Quoi et à quelle heure: _____
3. **Avez-vous enlevé le moniteur d'activité ?** __ Non __ Oui
   Si oui, de quelle heure à quelle heure? De _____ à _____
   Pourquoi ? _____

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Je suis heureux(se)
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Veuillez mettre un trait au centre de la ligne ci-dessous

_____

Autres évènements de la journée à indiquer :
.....
.....
.....
.....
.....

Heure :_____ Questionnaire du Matin 5

Heure:	Description d'alimentation
Déjeuner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **A quelle heure vous êtes vous couché(e) hier soir?** ____h____
2. **Combien de temps avez-vous pris pour vous endormir?**
   ❑ moins de 15 minutes ❑ 15 à 30 minutes ❑ 30 à 60 minutes ❑ 1 heure ou plus
3. **Vous êtes-vous réveillé(e) durant la nuit?** ❑ Non ❑ Oui
   Si oui, combien de fois ?__ Qu'est-ce qui vous a réveillé(e)?_____
4. **A quelle heure vous êtes-vous <u>reveillé(e)</u> pour de bon ce matin?** ____h____
5. **A quelle heure vous êtes-vous <u>levé(e)</u> ce matin ?** ____h____
6. **Sur une échelle de 1 (très mal dormi) à 5 (très bien dormi), entourez le chiffre correspondant le mieux à la qualité de votre sommeil:**
   1 2 3 4 5
   Très mal dormi Très bien dormi
7. **Sur une échelle de 1 (très fatigué(e), endormi(e), faible) à 5 (très en forme, éveillé(e), énergique), entourez le chiffre correspondent à votre forme au levé :**
   1 2 3 4 5
   Très fatigué(e) Très en forme

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis heureux(se)
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

Veuillez mettez un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ **Questionnaire du Midi 5**

Heure:	Description d'alimentation
Dîner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je sens que les gens ne m'aiment pas

Pas du tout _____ Tout à fait

Je suis heureux(se)

Pas du tout _____ Tout à fait

Je suis incapable de me détendre

Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots

Pas du tout _____ Tout à fait

Je parle moins que d'habitude

Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ Questionnaire du Soir 5

Heure:	Description d'alimentation
Souper:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **Avez-vous fait une sieste aujourd'hui?** __ Non __ Oui
   Si oui, de quelle heure à quelle heure? De _____ à _____
   Avez-vous dormi? _____
2. **Avez-vous fait des activités physiques aujourd'hui?** __ Non __ Oui
   Si oui: Quoi et à quelle heure: _____
3. **Avez-vous enlevé le moniteur d'activité ?** __ Non __ Oui
   Si oui, de quelle heure à quelle heure? De _____ à _____
   Pourquoi ? _____

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis heureux(se)
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Veuillez mettre un trait au centre de la ligne ci-dessous

_____

Autres évènements de la journée à indiquer :

.....
.....
.....
.....
.....

Heure :_____ Questionnaire du Matin 6

Heure:	Description d'alimentation
Déjeuner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **A quelle heure vous êtes vous couché(e) hier soir?** ____h____
2. **Combien de temps avez-vous pris pour vous endormir?**
   ❑ moins de 15 minutes ❑ 15 à 30 minutes ❑ 30 à 60 minutes ❑ 1 heure ou plus
3. **Vous êtes-vous réveillé(e) durant la nuit?** ❑ Non ❑ Oui
   Si oui, combien de fois ?__ Qu'est-ce qui vous a réveillé(e)?_____
4. **A quelle heure vous êtes-vous <u>reveillé(e)</u> pour de bon ce matin?** ____h____
5. **A quelle heure vous êtes-vous <u>levé(e)</u> ce matin ?** ____h____
6. **Sur une échelle de 1 (très mal dormi) à 5 (très bien dormi), entourez le chiffre correspondant le mieux à la qualité de votre sommeil:**
   1 2 3 4 5
   Très mal dormi Très bien dormi
7. **Sur une échelle de 1 (très fatigué(e), endormi(e), faible) à 5 (très en forme, éveillé(e), énergique), entourez le chiffre correspondent à votre forme au levé :**
   1 2 3 4 5
   Très fatigué(e) Très en forme

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Je suis heureux(se)
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Veuillez mettez un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ Questionnaire du Midi 6

Heure:	Description d'alimentation
Dîner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je parle moins que d'habitude

Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots

Pas du tout _____ Tout à fait

Je suis incapable de me détendre

Pas du tout _____ Tout à fait

Je suis heureux(se)

Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas

Pas du tout Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ Questionnaire du Soir 6

Heure:	Description d'alimentation
Souper:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **Avez-vous fait une sieste aujourd'hui?** __ Non __ Oui
   Si oui, de quelle heure à quelle heure? De _____ à _____
   Avez-vous dormi? _____
2. **Avez-vous fait des activités physiques aujourd'hui?** __ Non __ Oui
   Si oui: Quoi et à quelle heure: _____
3. **Avez-vous enlevé le moniteur d'activité ?** __ Non __ Oui
   Si oui, de quelle heure à quelle heure? De _____ à _____
   Pourquoi ? _____

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je suis heureux(se)
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Veuillez mettre un trait au centre de la ligne ci-dessous

_____

Autres évènements de la journée à indiquer :

.....
.....
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.....

Heure :_____ Questionnaire du Matin 7

Heure:	Description d'alimentation
Déjeuner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **A quelle heure vous êtes vous couché(e) hier soir?** ____h____
2. **Combien de temps avez-vous pris pour vous endormir?**

   ❑ moins de 15 minutes ❑ 15 à 30 minutes ❑ 30 à 60 minutes ❑ 1 heure ou plus
3. **Vous êtes-vous réveillé(e) durant la nuit?** ❑ Non ❑ Oui

   Si oui, combien de fois ?__ Qu'est-ce qui vous a réveillé(e)?_____
4. **A quelle heure vous êtes-vous <u>reveillé(e)</u> pour de bon ce matin?** ____h____
5. **A quelle heure vous êtes-vous <u>levé(e)</u> ce matin ?** ____h____
6. **Sur une échelle de 1 (très mal dormi) à 5 (très bien dormi), entourez le chiffre correspondant le mieux à la qualité de votre sommeil:**

   1 2 3 4 5

   Très mal dormi Très bien dormi
7. **Sur une échelle de 1 (très fatigué(e), endormi(e), faible) à 5 (très en forme, éveillé(e), énergique), entourez le chiffre correspondent à votre forme au levé :**

   1 2 3 4 5

   Très fatigué(e) Très en forme

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

Je suis heureux(se)
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ Questionnaire du Midi 7

Heure:	Description d'alimentation
Dîner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis incapable de me détendre

Pas du tout _____ Tout à fait

Je suis heureux(se)

Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots

Pas du tout _____ Tout à fait

Je parle moins que d'habitude

Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas

Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ Questionnaire du Soir 7

Heure:	Description d'alimentation
Souper:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **Avez-vous fait une sieste aujourd'hui?** __ Non __ Oui
   Si oui, de quelle heure à quelle heure? De _____ à _____
   Avez-vous dormi? _____
2. **Avez-vous fait des activités physiques aujourd'hui?** __ Non __ Oui
   Si oui: Quoi et à quelle heure: _____
3. **Avez-vous enlevé le moniteur d'activité ?** __ Non __ Oui
   Si oui, de quelle heure à quelle heure? De _____ à _____
   Pourquoi ? _____

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Je suis heureux(se)
Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Veuillez mettre un trait au centre de la ligne ci-dessous

_____

Autres évènements de la journée à indiquer :

.....
.....
.....
.....
.....

Heure :_____ Questionnaire du Matin 8

Heure:	Description d'alimentation
Déjeuner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **A quelle heure vous êtes vous couché(e) hier soir?** ____h____
2. **Combien de temps avez-vous pris pour vous endormir?**
   ❑ moins de 15 minutes ❑ 15 à 30 minutes ❑ 30 à 60 minutes ❑ 1 heure ou plus
3. **Vous êtes-vous réveillé(e) durant la nuit?** ❑ Non ❑ Oui
   Si oui, combien de fois ?__ Qu'est-ce qui vous a réveillé(e)?_____
4. **A quelle heure vous êtes-vous <u>reveillé(e)</u> pour de bon ce matin?** ____h____
5. **A quelle heure vous êtes-vous <u>levé(e)</u> ce matin ?** ____h____
6. **Sur une échelle de 1 (très mal dormi) à 5 (très bien dormi), entourez le chiffre correspondant le mieux à la qualité de votre sommeil:**
   1 2 3 4 5
   Très mal dormi Très bien dormi
7. **Sur une échelle de 1 (très fatigué(e), endormi(e), faible) à 5 (très en forme, éveillé(e), énergique), entourez le chiffre correspondent à votre forme au levé :**
   1 2 3 4 5
   Très fatigué(e) Très en forme

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots
Pas du tout _____ Tout à fait

Je suis heureux(se)
Pas du tout _____ Tout à fait

Je suis incapable de me détendre
Pas du tout _____ Tout à fait

Je parle moins que d'habitude
Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas
Pas du tout _____ Tout à fait

Veuillez mettre un trait <u>au centre</u> de la ligne ci-dessous

_____

Heure :_____ **Questionnaire du Midi 8**

Heure:	Description d'alimentation
Dîner:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis heureux(se)

Pas du tout _____ Tout à fait

Je parle moins que d'habitude

Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas

Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots

Pas du tout _____ Tout à fait

Je suis incapable de me détendre

Pas du tout _____ Tout à fait

Veuillez mettre un trait au centre de la ligne ci-dessous

_____

Heure:	Description d'alimentation
Souper:	
Collation:	

Heure:	Liste de médicaments (dosage)

Heure:	Nombre de cigarettes (ou cigares et/ou pipes) fumés

1. **Avez-vous fait une sieste aujourd'hui?** __ Non __ Oui
   Si oui, de quelle heure à quelle heure? De _____ à _____
   Avez-vous dormi? _____
2. **Avez-vous fait des activités physiques aujourd'hui?** __ Non __ Oui
   Si oui: Quoi et à quelle heure: _____
3. **Avez-vous enlevé le moniteur d'activité ?** __ Non __ Oui
   Si oui, de quelle heure à quelle heure? De _____ à _____
   Pourquoi ? _____

Veuillez répondre à ces questions en mettant un trait vertical entre les bornes « pas du tout » et « tout à fait »

Je suis incapable de me détendre

Pas du tout _____ Tout à fait

Je suis heureux(se)

Pas du tout _____ Tout à fait

J'ai des crises de larmes ou me sens comme si j'allais éclater en sanglots

Pas du tout _____ Tout à fait

Je parle moins que d'habitude

Pas du tout _____ Tout à fait

Je sens que les gens ne m'aiment pas

Pas du tout _____ Tout à fait

Veuillez mettez un trait au centre de la ligne ci-dessous

_____

Autres évènements à indiquer :

.....
.....

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Clinical Implication of Time of Day on Acute Exercise Response in COPD

Diurnal Variations in Psychological Distress in Chronic Obstructive Pulmonary Disease

Amplitude of the rest-activity cycle in chronic obstructive pulmonary disease: an exploratory study

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APPENDIX C – Other co-authored publication

Pepin V, Boucetta S, Chan-Thim E, Parwanta Z, Gouin JP, Dang-Vu T. The Role of Sleep and Physical Activity on the Risk for CVD. Current Cardiovascular Risk Report 2014, Sep; 8(12): 413

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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) ≥ 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 (≤ 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 1/3rd for men and 1/4th 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		Independent Variables		Dependent Variables
		N (M:F)	Descriptives	Sleep	Activity	
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		Independent Variables		Dependent Variables
		N (M:F)	Descriptives	Sleep	Activity	
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.

APPENDIX D – Regression analyses

Series of Regression models between depression severity and depressive symptoms, adjusted for measures of functional limitations (FEV_1, FEV_1/FVC, and W).

Depressive symptoms	**Unadjusted**		**Adjusted for FEV_1 (%Pred.)**		**Adjusted for FEV_1/FVC**		**Adjusted for exercise capacity (W)**	
	β	p	β	p	β	p	β	p
Positive affect	0.639	0.026	0.633	0.031	0.646	0.031	0.630	0.039
Depressed affect	0.836	0.025	0.820	0.032	0.844	0.030	0.955	0.030
Somatic complaints	1.386	0.001	1.362	0.001	1.386	0.001	1.448	0.001
Disturbed interpersonal relationships	1.460	0.001	1.433	0.001	1.455	0.001	1.606	0.001