School of Physiotherapy and Exercise Science

Quantifying Dyspnoea and Physical Activity in Saudi Nationals with Chronic Obstructive Pulmonary Disease in Riyadh, Saudi Arabia

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DECLARATION

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

Signature: 

Date: 07/08/2015

STATEMENT OF ORIGINALITY

This thesis is presented for the degree of Doctor of Philosophy at Curtin University, Western Australia. Studies were undertaken between August 2011 and August 2015, through the School of Physiotherapy and Exercise Science at Curtin University, in association with the Respiratory Department at King Fahad Medical City in Riyadh, Saudi Arabia.

All of the material presented in this thesis is original. This program of research was developed in association with my supervisors who have been involved in editing both this thesis and an associated publication.

ABSTRACT

Background and research questions

The Dyspnoea-12 (D-12) is a short questionnaire that consists of 12 items relevant to assessing dyspnoea in people with a variety of cardiopulmonary diseases. It measures the severity of dyspnoea in terms of the quality of sensation and the emotional response that the dyspnoea evokes. Each item is rated 'none' (score = 0), 'mild' (score = 1), 'moderate' (score = 2) or 'severe' (score = 3). The total scores of the D-12 range from 0 to 36, with higher scores representing greater severity of dyspnoea. The D-12 has been shown to be reliable and valid in people with chronic obstructive pulmonary disease (COPD), interstitial lung disease, asthma and pulmonary hypertension.

In Saudi nationals, this program of research was designed to address the following research questions:

1. Is the Arabic version of the D-12 reliable and valid in Saudi nationals with COPD?

2. Do the quality and emotional response components of the D-12 differ between periods of an AECOPD and periods of clinical stability?

3. Do physical activity and sedentary behaviour in males with COPD differ from those of healthy controls?

4. Are the quality and emotional response components of the D-12 associated with physical activity and sedentary behaviour in males with COPD?

Study 1 (addressing the first research question)

Methods

This study was a cross-sectional study comprised of two parts (A and B). Part A involved the translation of the D-12 into the Arabic language, through a process of forward-backward translation. The Arabic version developed in part A was administered to five participants with COPD to test whether it was easily understood after which a final Arabic version was produced. In part B, participants completed

the D-12, the COPD Assessment Test (CAT), the Chronic Respiratory Disease Questionnaire (CRDQ), the six-minute walk test (6MWT) and spirometric measures of lung function. The participants in part B repeated the D-12 two weeks after the first administration. An intraclass correlation coefficient (ICC) was used to assess test–retest reliability in the entire sample and also with participants grouped according to their disease severity. The weighted kappa coefficient was used to determine the concordance of the responses between the first and second administrations of the D-12. The ICC was also used to assess test-retest reliability of the D-12 for participants grouped according to their disease severity. Pearson's correlation coefficients were performed to assess construct validity of the D-12 scores by examining the strength of associations between the D-12 and the CAT, CRDQ, six-minute walk distance (6MWD) and post-bronchodilator forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). The total scores for the D-12 with participants grouped according to their GOLD grades were compared using analysis of variance. All data are expressed as mean ± standard deviation (SD) unless otherwise stated.

Results

In part A, there were no differences between the back-translated version of the D-12 and the original English version. Five participants (four males, 80%) aged 65.0 ± 10.0 years with a FEV_1 of 51 ± 19% predicted reported that all items of the Arabic version of the D-12 were easily understood and no comments were reported by the participants. For part B, data were collected for 40 participants (33 males, 83%) aged 63.0 ± 9.0 years with a FEV_1 % of 47 ± 16% predicted. The ICC for the Arabic version of the D-12 over the two administrations was 0.94 ($p = 0.01$), and the weighted kappa value was 0.83. The ICC for the reliability of the D-12 score for the participants grouped according to their disease severity was 0.90 for moderate disease, 0.97 for severe disease and 0.85 for very severe disease (all $p < 0.01$).

The mean scores for 10 of the D-12 items were no different between the two administrations and the mean scores of the remaining two D-12 items differed by less than one point. Strong associations were demonstrated between the: (i) total score for the D-12 and the CAT, (ii) quality component of the D-12 and the CAT and (iii) emotional response component of the D-12 and the emotional function domain of the

CRDQ ($r \geq 0.6$, all $p < 0.01$). Associations of weak to moderate strength were demonstrated between the (i) total score of the D-12 and both 6MWD and FEV_1, (ii) quality component of the D-12 and the dyspnoea domain of the CRDQ, FEV_1, FVC and 6MWD and (iii) emotional response component of the D-12 and all domains of the CRDQ and CAT ($r \geq 0.31$, all $p < 0.05$). The total D-12 score differed between participants with moderate and very severe COPD (mean difference = 4.6 ± 4.9; $p < 0.01$).

Discussion and conclusion

This study successfully translated the D-12 to the Arabic language. Similar results were found in a study that translated the D-12 into Korean. The total score for the D-12 was reliable over a two-week period, as demonstrated by the high values of ICC and weighted kappa. In addition, the scores obtained on the D-12 for people who were grouped according to disease severity were reliable, as indicated by the ICC values ≥ 0.85 for those with moderate to very severe COPD. In the present study, the ICC value was similar to those values reported in earlier work in which the D-12 was administered twice over the same period in populations with COPD (ICC = 0.90), asthma (r = 0.93 to 0.96) and interstitial lung disease (ICC = 0.94). The Arabic version of the D-12 is valid in Saudi nationals with COPD, as strong associations were reported between the D-12 components and its total score with the scores of questionnaire-based assessments. The differences in the total score of the D-12 between people with moderate and very severe COPD supports the validity of the D-12. The weak to moderate associations between the total score of the D-12 and both the 6MWD and the FEV_1 is consistent with previous studies undertaken in people with COPD and asthma, and indicates that dyspnoea worsens with increased functional limitation and disease severity. The D-12 is likely to be a useful tool for assessing dyspnoea in the clinical and research setting.

Study 2 (addressing the second research question)

Methods

This was a longitudinal observational study that included participants who were admitted to hospital with an AECOPD. Within 24 hours of hospitalisation, all participants completed a set of questionnaires that comprised the D-12, CAT and

CRDQ. This set of questionnaires was repeated every 14 days until 98 days following hospital admission. This resulted in a total of eight administrations for each questionnaire. Each time the questionnaires were completed after the first administration in hospital, the participants were asked a standard question to determine whether or not they had experienced a re-exacerbation. The standard question asked was: 'Has there been any change in your symptoms over the last two weeks that required you to increase your medication use or to visit a doctor or the hospital?' To characterise the participants, measures of spirometry were obtained at the time they were discharged from the hospital.

Changes were explored in both the quality and emotional response components of the D-12 between the first administration in hospital and the time period during the 98 day follow-up when the participants were deemed to have returned to clinical stability. For this purpose, clinical stability was defined as being when the magnitude of change in the dyspnoea domain of the CRDQ between consecutive administrations was neither statistically significant nor clinically important (i.e. change was < 0.5 points per item [ppi]).

Effect sizes were calculated to facilitate comparison of the magnitude of the change in the score of each questionnaire between first administration in hospital and the time when participants were deemed to have returned to clinical stability. The effect size for each questionnaire was calculated as the mean difference in scores reported during the first administration in hospital and clinical stability, divided by the standard deviation obtained at the first administration in hospital.

During the first administration in hospital and also during the period when participants had returned to clinical stability, scores of the total, quality and emotional response components the D-12 were compared between participants grouped according to their disease severity. All data are expressed as mean ± SD unless otherwise stated.

Results

Twenty-nine participants (25 males, 86%) aged 64.9 ± 3.9 years with a FEV_1 of 44 ± 11% predicted completed the study. The group met the criteria for clinical stability 70 days after the first administration in hospital. This was because the scores in the

dyspnoea domain of the CRDQ completed 70, 84 and 98 days after the first administration in hospital did not differ statistically and the magnitude of difference was below the threshold for clinical importance (mean scores 3.7 ± 0.6, 3.7 ± 0.7 and 3.7 ± 0.7 ppi, respectively, $p > 0.05$). Compared with the scores reported during the first administration in hospital, when the group had returned to clinical stability there was a decrease (i.e. improvement) in the total score of the D-12 (26.3 ± 3.0 *versus* 20.1 ± 2.9; $p < 0.001$), the quality component (15.3 ± 2.2 *versus* 11.8 ± 1.5; $p < 0.001$), and the emotional response (11.0 ± 2.0 *versus* 8.3 ± 1.6; $p < 0.001$). Similarly, compared with the scores reported during the first administration in hospital, when the group had returned to clinical stability there was an increase (i.e. improvement) in the scores for the dyspnoea domain of the CRDQ (2.7 ± 0.4 *versus* 3.7 ± 0.7; $p < 0.001$) and a decrease (i.e. improvement) in the score for the CAT (26.2 ± 2.0 *versus* 20.2 ± 3.9; $p < 0.001$).

Effects sizes for the change in scores reported during the first administration in hospital and when the group had returned to clinical stability were larger for the CAT (effect size = 3.0) compared with the dyspnoea domain of the CRDQ (effect size = 2.5), total score for the D-12 (effect size 2.1) as well as the quality component (effect size = 1.6) and emotional response component (effect size = 1.7).

During the first administration in hospital, the total D-12 score differed between participants with moderate and very severe COPD (mean difference = 5.3 ± 1.4, $p = 0.006$), and between participants with severe and very severe COPD (mean difference = 4.2 ± 3.4, $p = 0.006$). Similarly, the score of the emotional response component of the D-12 differed between participants with moderate and very severe COPD (mean difference = 3.0 ± 1.1, $p = 0.002$), and between participants with severe and very severe COPD (mean difference = 1.8 ± 0.9, $p = 0.019$).

During the period when participants had returned to clinical stability, the total D-12 score differed between participants with moderate and very severe COPD (mean difference = 4.4 ± 2.0, $p = 0.037$). Similarly, the score of the emotional response component of the D-12 differed between participants with moderate and very severe COPD (mean difference = 2.6 ± 1.8, $p = 0.011$).

Discussion and conclusions

This study demonstrated that overall, following hospitalisation with an AECOPD, recovery, in terms of no further improvement in dyspnoea during activities of daily living, can take up to 70 days. Scores obtained from all questionnaires improved significantly between when participants were hospitalised with an AECOPD and when they had reached a period of clinical stability. The large mean differences coupled with the small variability in the magnitude of these differences accounted for the large effect sizes demonstrated in this study. The questionnaire that was most responsive to change was the CAT, which demonstrated an effect size of 3.5. The most likely reason that the responsiveness of the CAT was greater than that of the D-12 is that the CAT comprises items related to a broad range of factors that are likely to be adversely impacted during an AECOPD, such as sleep quality and energy levels, rather than just dyspnoea. The total score of the D-12 and the emotional response component of the D-12 discriminated between people with COPD grouped according to their disease severity during the first administration in hospital and when they had returned to clinical stability. This finding supports the validation of the D-12 in people with stable COPD. Given that the effect size for the D-12 was similar to the effect size for the dyspnoea domain of the CRDQ (effect size 2.1 *versus* 2.5) it is possible that the D-12 will demonstrate similar responsiveness to the CRDQ following interventions that aim to ameliorate dyspnoea such as bronchodilators and pulmonary rehabilitation.

Study 3 (addressing the third and fourth research questions)

Methods

This study was a cross-sectional, observational study that included males with COPD and healthy controls. Participants were instructed to wear the StepWatch^{TM} Activity Monitor (SAM) during their waking hours for eight consecutive days. The SAM records the number of steps taken and provides data in one-minute epochs. Measures of spirometry were obtained for both groups. The 6MWT was completed by participants with COPD. Step counts derived from the SAM were exported to Microsoft Excel to derive the time spent in two major domains: (i) walking based activity (defined as $\geq$ 1 step/minute [steps/min]) and (ii) sedentary behaviour

(defined as 0 steps/min). Thereafter, walking based activity was divided into cadence bands suggested by the National Health and Nutrition Examination Survey study as follows: 1 to 19, 20 to 39, 40 to 59, 60 to 79, 80 to 99, 100 to 119 and ≥ 120 steps/min. Data pertaining to the time spent undertaking walking based activity and sedentary behaviour were averaged over the duration of the wear period (one week) and were compared between groups. The duration of every bout of walking based activity and every bout of sedentary behaviour recorded over the duration of the wear period were averaged and were compared between groups. For each participant, the peak (the one-minute epoch during which the highest cadence was recorded) and average 30-minute peak cadence (the average of the 30 individual one-minute epochs, during which the highest cadences were recorded, not necessarily consecutively) were obtained for each day over the entire wear period and were averaged. Thereafter, the following variables were compared between groups: (i) the peak cadence and, (ii) the average 30-minute peak cadence. The proportion of participants with COPD and healthy controls who met the threshold of 7,000 steps per day over five or more days, as suggested by the guidelines of American College of Sports and Medicine were compared. In participants with COPD, associations were examined between the scores of quality and emotional response components of the D-12 with time spent in walking based activity and sedentary behaviour.

Results

Thirty males with COPD (age 62.0 ± 5.0 years; FEV_1 46 ± 15% predicted) and 29 gender-matched healthy controls (age 63.0 ± 4.3 years; FEV_1 91 ± 5% predicted) completed the study. No differences were seen between participants with COPD and healthy controls in the number of days of SAM data (6.8 ± 0.5 days [COPD participants] *versus* 6.9 ± 0.3 days [healthy participants]; $p = 0.36$), or in the average daily wear time (13.4 ± 0.8 hours/day [COPD participants] *versus* 13.5 ± 0.5 hours/day [healthy participants]; $p = 0.40$).

Compared with the healthy controls, participants with COPD spent a lower percentage of their waking hours in walking based activity (37 ± 7% *versus* 22 ± 8%; $p < 0.001$) and a higher percentage of time in sedentary behaviour (63 ± 6% *versus* 78 ± 8%; $p < 0.001$). This difference was equivalent to 131 ± 105 minutes fewer minutes and 109 ± 103 additional minutes a day for walking based activity and

sedentary behaviour, respectively. Compared with the healthy controls, participants with COPD spent a lower percentage and fewer minutes accumulating walking based activity in all cadence bands except those ≥ 100 steps/min, $p > 0.05$.

Compared with the healthy controls, participants with COPD accumulated time in walking based activity in shorter bouts (6 ± 1 *versus* 3 ± 1 min/day; $p < 0.01$) and sedentary behaviour in longer bouts (9 ± 2 *versus* 12 ± 2 min/day; $p < 0.01$). The peak cadence was lower in participants with COPD than healthy controls (76 ± 13 *versus* 93 ± 13 steps/min; $p < 0.01$). The average 30-minute peak cadence was lower in participants with COPD compared with healthy controls (47 ± 11 *versus* 62 ± 9 steps/min; $p < 0.01$). Compared with healthy controls, the proportion of participants with COPD who met the criteria for participating in sufficient walking based activity (7,000 steps per day in five or more days) was lower (34 % *versus* 7%; $p < 0.001$).

Moderate associations were demonstrated between the quality score of the D-12 and time spent in walking based activity ($r \geq -0.52$, $p < 0.01$) and sedentary behaviour ($r \geq 0.46$, $p < 0.01$). Strong associations were observed between the emotional response score of the D-12 and time spent in walking based activity ($r \geq -0.63$, $p < 0.01$) and sedentary behaviour ($r \geq 0.66$, $p < 0.01$).

Discussion and conclusion

The findings of this study demonstrate that, compared to healthy controls, males with COPD spent less time in walking based activity and more time in sedentary behaviour. These findings correspond to previously reported work conducted in Belgium and Brazil. In the present study, males with COPD spent less time in cadence bands < 100 steps/min when compared with healthy controls. High cadences (≥ 100 steps/min) have been considered a threshold for moderate intensity physical activity in adults. However, neither males with COPD nor the healthy controls in this study participated in walking based activity at cadences ≥ 100 steps/min, which explains the lack of difference between them in these cadence bands. These findings suggest that males with COPD as well as healthy controls in Saudi Arabia may be at greater risk of developing chronic diseases, such as cardiovascular and metabolic diseases, as they do not spend time participating in daily moderate intensity physical activity Therefore, these findings suggest that awareness of the benefits of walking

based activity and physical activity needs to be promoted among the general public as well as people with COPD in Saudi Arabia.

Compared to healthy controls, males with COPD accumulated time in walking based activity in shorter bouts and sedentary behaviour in longer bouts. It is likely that the exercise impairment in COPD impacts the way people distribute their time of activity over a day, with long bouts of sedentary behaviour and shorter bouts of walking based activity. These findings highlight the importance of educate people with COPD to spend longer duration in bouts of physical activity for the purpose of health benefits. The peak and average 30-minute cadence were lower in males with COPD compared to that observed in the healthy controls. This reduction in peak cadences of walking based activity in males with COPD may reflect their limitation of peak aerobic capacity. Compared to healthy controls, the proportion of males with COPD (7%) who accumulated ≥ 7,000 steps/day was lower than that observed in healthy controls (34%). These findings increase the importance of designing interventions that aim to increase daily steps in males with COPD to meet the recommended amount of physical activity necessary to confer health benefits.

This study demonstrated associations of moderate strength between the quality component of the D-12 with the time spent in walking based activity ($r \geq -0.52$) and sedentary behaviour ($r \geq 0.46$). However, the emotional response component of D-12 yielded somewhat stronger associations with the time accumulated in walking based activity ($r \geq -0.63$) and sedentary behaviour ($r \geq 0.66$). The associations demonstrated in this study extend the results reported in both Study 1 and Study 2 which pertain to the validity of the D-12 in people with COPD. This is the first study to examine and report the associations between the components of the D-12 and walking based activity and sedentary behaviour in males with COPD. The results of this study highlight the importance of targeting an intervention that aims to minimise the emotional response of dyspnoea, which may result in reducing the time spent in sedentary behaviour and optimising participation in daily physical activity.

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PUBLICATIONS, PRESENTATIONS AND AWARDS

Alyami MM, Jenkins SC, Lababidi H, Hill K. Reliability and validity of an Arabic version of the dyspnea-12 questionnaire for Saudi nationals with chronic obstructive pulmonary disease. *Annals of Thoracic Medicine*. 2015;10(2):112-117.

Manuscripts in preparation

Alyami MM, Jenkins S, Hill K. Changes in the Dyspnoea-12 questionnaire following an acute exacerbation of chronic obstructive pulmonary disease.

Alyami MM, Jenkins S, Hill K. Physical activity and sedentary behaviour in Saudi males with chronic obstructive pulmonary disease.

Presentations arising from this thesis

Alyami MM, Jenkins SC, Lababidi H, Hill K. Measurement Properties of an Arabic Version of the dyspnea-12 questionnaire for Saudi Nationals with chronic obstructive pulmonary disease. Poster oral presentation at the Gulf Thoracic Congress Annual Scientific Meeting in Dubai, 2014.

Awards

Best abstract presentation at the Gulf Thoracic Congress Annual Scientific Meeting

Awarded at the Gulf Thoracic Congress Annual Scientific Meeting in Dubai, 2014 for excellent work and winning the first place of the Annals of Thoracic Medicine Best Abstract Award.

LIST OF ABBREVIATIONS

%	percentage
6MWD	six-minute walk distance
6MWT	six-minute walk test
ACSM	American College of Sports Medicine
AECOPD	acute exacerbation of chronic obstructive pulmonary disease
ANOVA	analysis of variance
BDI	Baseline Dyspnoea Index
BMI	body-mass index
BODE	Body-mass index, airflow Obstruction, Dyspnoea and Exercise capacity index
BOLD	the Burden of Obstructive Lung Disease
CAT	Chronic obstructive pulmonary disease Assessment Test
CI(s)	confidence interval(s)
COPD	chronic obstructive pulmonary disease
CRDQ	Chronic Respiratory Disease Questionnaire
D-12	Dyspnoea-12 questionnaire
FEV_1	forced expiratory volume in one second
FEV_1/FVC	the ratio of forced expiratory volume at one second to forced vital capacity expressed as a percentage
FVC	forced vital capacity
g	grams
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HADS	Hospital Anxiety and Depression Scale
HRQoL	health-related quality of life
Hz	Hertz
ICC	intraclass correlation coefficient
ILD	interstitial lung disease
kg/m^2	kilograms per meters squared
L	liters
m	meter
MARCA	Multimedia Activity Recall for Children and Adults
MCID	minimal clinically important difference
MDP	Multidimensional Dyspnoea Profile
METs	metabolic equivalent units
min	minute
mMRC	modified Medical Research Council
MRC	Medical Research Council
n	number of participants in the study
O_2	oxygen
OCD	oxygen cost diagram
OR	odds ratio

p	probability
PAR	Physical Activity Recall questionnaire
PFSDQ-M	Pulmonary Functional Status and Dyspnoea Questionnaire-Modified version
ppi	points per item
pred	predicted
r	correlation
SAM	Stepwatch^{TM} Activity Monitor
SD	standard deviation
SF-36	36-Item Short Form Health Survey
SGRQ	St. George's Respiratory Questionnaire
SOBQ	San Diego Shortness of Breath Questionnaire
SpO_2	percutaneous oxygen saturation
SPSS	Statistical Package for the Social Sciences
TDI	Transitional Dyspnoea Index
VAS	visual analogue scale

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CHAPTER 1

INTRODUCTION

This program of research focuses on the assessment of dyspnoea in people with chronic obstructive pulmonary disease (COPD) in Saudi Arabia. All studies were undertaken in Riyadh, Saudi Arabia.

In Saudi Arabia, the prevalence of COPD was estimated at 2.4%,being more prevalent in males (3.5%) than females (1.0%) (1). This is similar to the prevalence reported for the Middle East (3.6%) (1). A Saudi study among smokers aged ≥ 40 years found that 14.2% had COPD, similar to the prevalence in smoking populations in Turkey (18.1%) (2, 3). The prevalence rate of COPD in Saudi Arabia is lower than that reported in many other countries: 26.1% in Austria (4), 24.0% the Netherlands (5), 20.8% in the Philippines (6), 16.2% in Sweden (7), 7.9% in Australia (8) and 8.2% in China (9).

Smoking is the primary risk factor in the development of COPD (10). The smoking rate in the Saudi population is 28.0% among those aged ≥ 40 years, with a rate of 39.0% in males and 7.0% in females (11). The prevalence of COPD is therefore expected to increase even further (2). Other risk factors in the development of COPD in Saudi Arabia include outdoor air pollution, desert dust, wars and childhood respiratory infections (12).

Dyspnoea (breathlessness) is a term used to describe a sensation of breathing discomfort that comprises distinct sensations that vary in quality and intensity (13). For people with COPD, dyspnoea is often the primary symptom that limits daily activities and leads to a decrease in health-related quality of life (HRQoL) (10, 14). There are several methods used to measure an individual's perception of dyspnoea in COPD. However, these measurement options are often unidimensional assessments and may not be available in Arabic with the result being that there is little work on the measurement of dyspnoea of people with COPD in Saudi Arabia.

A plethora of tools for the measurement of dyspnoea exist and the majority of tools have been validated in COPD populations (15, 16). Measuring dyspnoea in people with COPD can be done using unidimensional tools, multidimensional tools, and

dyspnoea may be embedded within HRQoL questionnaires. The unidimensional tools can assess dyspnoea directly, using the modified Borg or visual analogue scales (17, 18), in people experiencing dyspnoea at rest or in response to different stimuli. Furthermore, the unidimensional tools can evaluate dyspnoea indirectly, using the Medical Research Council Questionnaire (19), by asking the respondent to report functional limitation resulting from dyspnoea. However, the unidimensional tools may not be adequate enough to capture the complexity of dyspnoea. The common multidimensional tools, such as the Baseline and the Transitional Dyspnoea Index, and the Pulmonary Functional Status and Dyspnoea Questionnaire—Modified version (20, 21), measure different activities that cannot be accomplished due to dyspnoea. Although multidimensional tools provide useful information, they do not measure dyspnoea components such as the emotional response to dyspnoea; they measure the impact of dyspnoea on activities. Using dyspnoea embedded within HRQoL questionnaires, like the Chronic Respiratory Disease Questionnaire (22), provides information about the impact of dyspnoea on HRQoL. This also means that they cannot quantity different components of dyspnoea. The Dyspnoea-12 questionnaire (D-12) is a multidimensional tool that measures the severity of dyspnoea and considers both the quality of the sensation and the emotional response that it evokes (23). This questionnaire was derived following a literature search of the descriptors used to describe dyspnoea by people with cardiorespiratory diseases (23). Descriptions of the measurement of dyspnoea are provided in Chapter 2; Section 2.3.3.

One of the overall purposes of this program of research was to provide clinicians and researchers working in Saudi Arabia with a simple and valid tool to measure dyspnoea in people with COPD. To achieve this purpose, the D-12 was translated into Arabic and the reliability and validity of this version was assessed. Further, data are reported which demonstrate the capacity of the D-12 to both change in response to a change in clinical status and discriminate between people with COPD grouped according to the severity of their condition. A second purpose of this program of research was to compare physical activity levels and the time spent in sedentary behaviour in Saudi nationals with COPD with healthy controls. This comparison is important as it will assist health professionals in Saudi Arabia to understand the lifestyle of their patients. In addition, data are reported which explore the

associations between the D-12 and physical activity levels and sedentary behaviour in COPD. This provided further support for the validation of the D-12. It also assisted in determining to what extent physical activity and sedentary behaviour are influenced by dyspnoea in Saudis with COPD. The current chapter provides a rationale for the development of each research question. The significance and novelty of each component in the program of research are also discussed.

1.1 Research aims

In Saudi nationals, this program of research was designed to: (i) translate the D-12 into the Arabic language and investigate the reliability and validity of an Arabic version of the D-12 in people with COPD; (ii) determine whether the quality and emotional response components of the D-12 differed between a period when people were hospitalised with an acute exacerbation of COPD (AECOPD) and when they had reached a period of clinical stability following hospital discharge; (iii) compare physical activity and sedentary behaviour in males with COPD with age and gender-matched healthy controls and, (iv) report associations between the quality and emotional components of the D-12 with physical activity and sedentary behaviour in males with COPD.

1.2 Research Aim 1

To translate the D-12 into the Arabic language and investigate the reliability and validity of an Arabic version of the D-12 in people with COPD.

1.2.1 Research hypotheses

The primary hypothesis was: the D-12 will be reliable and valid in Saudi nationals with COPD.

The secondary hypothesis was: the D-12 will be reliable in people with COPD grouped according to disease severity.

1.2.2 Background

For people with COPD, dyspnoea is often the most distressing symptom and main complaint when seeking medical assistance (24, 25). Dyspnoea refers to an uncomfortable and inappropriate sensation of breathing that results from the interaction of multiple physiological, psychological, social and environmental factors (13). In people with COPD, dyspnoea has been found to be a strong predictor for mortality (26). Similar to pain, the sensation of dyspnoea can be described in terms of its intensity, quality of the sensation and the emotional response to dyspnoea (27, 28).

The assessment of dyspnoea is usually focused on the severity or intensity of the sensation, and this is often evaluated using unidimensional assessment tools, such as the modified Borg scale (17) and the visual analogue scale (18). Currently, however, there is increased recognition of the importance of the quality of sensation (29-31). Specifically, it has been observed that the quality of dyspnoea varies between people with different cardiopulmonary diseases (32). For example, the descriptor ‘chest tightness’ is most frequently described by people with asthma (29, 32, 33), while the descriptors ‘increased work’ and ‘effort of breathing’ are more often used by people with COPD (29, 33, 34). These differences suggest that the sensations have different pathophysiological origins. For instance, in asthma, ‘chest tightness’ appears to result from bronchoconstriction (35). In contrast, in COPD, ‘increased work’ and ‘effort of

breathing' may refer to the deleterious effects of pulmonary hyperinflation, which serves to increase the elastic and threshold loads borne by the inspiratory muscles, thus reducing their mechanical advantage (36, 37).

In addition to the differences in intensity and quality of the sensation, dyspnoea often evokes considerable emotional distress, such as feelings of anxiety and panic (38). These mood disturbances increase disability, functional impairment and reduce HRQoL (39). Given the complexity of dyspnoea, there is an interest in developing instruments that assess the intensity of dyspnoea as well as its quality and the emotional response to this sensation. Yorke et al (23) developed the D-12 to quantify these three components of dyspnoea. In people with COPD, the D-12 demonstrated good test–retest reliability (intra-class correlation coefficient [ICC] = 0.9, $p < 0.001$) and construct validity (23). Similar observations have been demonstrated in people with asthma, interstitial lung disease and pulmonary arterial hypertension (40-42). The D-12 is available in different languages, such as Korean and Japanese (43, 44). However, at the time this study was initiated, there was no Arabic version available.

1.2.2.1 Significance and novelty of the research

Increasing recognition that dyspnoea varies in terms of the severity, quality and emotional response that it evokes necessitates a valid and reliable method of assessing these components of the sensation. This study will be the first to translate the D-12 into the Arabic language and establish the reliability and validity of the D-12 in the Arabic language. The Arabic language version of D-12 will facilitate a means by which clinicians and researchers can assess dyspnoea in both Saudi nationals with COPD, but also in any Arabic Gulf COPD population as these Gulf countries have a similar culture. This is an important step to promote the implementation of therapies in Arabic Gulf countries, including Saudi Arabia, such as pulmonary rehabilitation, which has achieved strong evidence for reducing dyspnoea in people with COPD (45).

1.3 Research Aim 2

To determine whether the quality and emotional response components of the D-12 differed between a period when people were hospitalised with an AECOPD and when they had reached a period of clinical stability following hospital discharge.

1.3.1 Research hypotheses

The primary hypothesis was that the quality and emotional response components of the D-12 will change between periods of an AECOPD and periods of clinical stability.

The secondary hypothesis was that during an AECOPD and also a period of clinical stability, the quality and emotional response components of the D-12 will discriminate between people with COPD, grouped according to disease severity.

1.3.2 Background

In order to optimise the use of the D-12 in clinical practice, there is a need to demonstrate that it can change in response to an intervention or clinical event that changes dyspnoea. Simple, unidimensional tools that measure dyspnoea, such as the Borg scale and visual analogue scale, have been shown to change following interventions such as pulmonary rehabilitation, and long-acting bronchodilators, and clinical events such as an AECOPD (24, 46-48). At the beginning of this program of research, consideration was given to assessing changes in the quality and emotional response components of the D-12 in response to pulmonary rehabilitation or bronchodilator therapy. Although pulmonary rehabilitation is known to be effective in reducing dyspnoea in people with COPD (45), in Saudi Arabia, pulmonary rehabilitation is generally in its infancy (49) and is not widely available. The use of long-acting bronchodilator therapy was not considered to be appropriate as an intervention to change dyspnoea. This was because these medications are considered to be a standard component of care for people with COPD (10) and therefore, finding an adequate number of people who were naïve to these medications was deemed to be unrealistic in the time frame available to complete these studies. The use of short-acting bronchodilator therapy was not considered to be appropriate as the effect of these medications on dyspnoea is inconsistent in people with COPD (50-52). An AECOPD is an event characterised by a sustained worsening of the respiratory symptoms of an individual, from the stable state and beyond normal day-to-day variations, that is acute at onset and necessitates a change in regular medication (10). In people with COPD, an increase in dyspnoea is often the reason for seeking medical attention during an AECOPD (25). Earlier work has shown that the changes

in dyspnoea during and following an AECOPD are large (24, 53). For example, Aaron et al (53) and Parker et al (24) assessed dyspnoea, using the dyspnoea domain of the Chronic Respiratory Disease Questionnaire (CRDQ), during and following a moderate to severe AECOPD. The authors showed a significant increase (i.e. improvement) of ≥ 1.3 points per item (ppi) in the score of the dyspnoea domain of the CRDQ following periods of an AECOPD. This magnitude of change in the score of the dyspnoea domain of the CRDQ following an AECOPD represents a large clinical improvement. Further, following an AECOPD, the dyspnoea domain of the CRDQ produced a large effect size (53).

To date, no study has explored or reported the responsiveness of the D-12 to a change in clinical status that impacts on dyspnoea, such as hospitalisation for a severe AECOPD.

1.3.2.1 Significance and novelty of the research

The responsiveness of the D-12 to change in clinical status is unknown and therefore, this study will be the first to report whether the D-12 is responsive to a change in clinical status during a period of recovery following a severe AECOPD. Data demonstrating the capacity of the D-12 to change when dyspnoea changes is needed before the D-12 can be widely used to evaluate dyspnoea in clinical practice and research. The findings from this research will also determine which components (quality and/or emotional response) of dyspnoea are most affected during an AECOPD. If there is a difference in the responsiveness between these components this will be the first study to report such a finding. Furthermore, this study will report the responsiveness of other tools in this setting (i.e. the CRDQ and COPD Assessment Test [CAT]) and will therefore allow the responsiveness of the D-12 to be compared with these other questionnaires. The findings from this research will provide a basis on which clinicians and researchers can select the most responsive questionnaires to use in people with COPD. Finally, the results of this study will be the first to report data on the characteristics and pattern of recovery in Saudi nationals who are hospitalised with an AECOPD. This will provide insight regarding the expected time course of recovery and assist clinicians in providing patients and their families information about this.

1.4 Research Aim 3

To compare physical activity and sedentary behaviour in people with COPD with age and gender-matched healthy controls.

1.4.1 Research hypothesis

The hypothesis was that physical activity and sedentary behaviour will be different between people with COPD and healthy controls.

1.4.2 Background

Guidelines from the United States of America recommend that adults need to participate in moderate to vigorous intensity physical activity (i.e. activities that require an energy expenditure ≥ 3 metabolic equivalent units [METs]) to confer health benefits (54). In adult populations, the health benefits of regular participation in moderate to vigorous intensity physical activity have been demonstrated to include reductions in the risk of cardiovascular and metabolic disease, weight loss, lowered blood pressure, greater insulin sensitivity as well as lower all-cause mortality (54).

People with COPD perform very little physical activity (55, 56). Several studies have demonstrated that people with COPD participate in less physical activity when compared with healthy controls (55-57). Data pertaining to physical activity in people with COPD have demonstrated that, on average, the percentage of time people with COPD spent participating in physical activity, relative to healthy controls, was 57% (58). In people with COPD, participating in lower levels of physical activity has been associated with several factors (59). These factors include higher dyspnoea severity, greater disease severity and static lung hyperinflation, less autonomous motivation for exercise, lower exercise capacity, worse leg muscle function, using long term oxygen therapy, a higher number of exacerbations in the past year and greater feelings of depression (59).

To date, most studies that have explored the health benefits of physical activity have focused on moderate and vigorous intensity physical activity. However, there is now increased recognition of the possible health benefits associated with accumulating time in light intensity physical activity such as reducing the risk of developing

cardiovascular disease and type-II diabetes (60, 61). This is likely to be particularly relevant to people with COPD given that they are often unable to participate in moderate or vigorous intensity physical activity due to intolerable dyspnoea (57).

Although there are several methods available to quantify the intensity of physical activity undertaken during daily life, cadence (steps/minute) is a walking parameter that is considered a logical surrogate of intensity (62, 63). Several laboratory-based studies have reported increasing intensity with increasing cadence such that ≥100 steps/minute seems to be a threshold equivalent to moderate to vigorous intensity physical activity (equivalent to ≥ 3 METs) in adults (62, 64-66). Investigators from the National Health and Nutrition Examination Survey proposed incremental cadence bands that range from 0 (i.e. sedentary) to ≥ 120 steps/minute (i.e. vigorous intensity) to explore differences in the intensity of physical activity amongst the population of the United States of America (67). Using these incremental bands in people with COPD will provide detailed information regarding their patterns of daily physical activity in terms of time accrued in different cadence bands.

Sedentary behaviours are defined by activities or behaviours that require low energy expenditure (< 1.5 METs) throughout waking hours and undertaken in sitting or reclining postures (68). In the general adult population, excessive sedentary time has been associated with a greater risk for all-cause mortality, independent of time spent in moderate to vigorous physical activity (69). In people with COPD, besides participating in low levels of physical activity, a large amount of their waking hours are spent in sedentary behaviour. Compared to healthy controls, people with COPD spend around 40% more time of their waking hours in sitting and reclining postures (56, 70). In people with COPD, sedentary behaviour is associated with factors including lower exercise capacity, less autonomous motivation for exercise, a higher number of AECOPDs in the past year and using long term oxygen therapy (59). To date, little is known about the health consequences of sedentary behaviour in people with COPD. It is likely that the deleterious outcomes demonstrated in the general population including the risk of developing metabolic and cardiovascular diseases or dying prematurely also apply to people with COPD (56, 57).

In addition to looking at the total time spent participating in physical activity and sedentary behaviour, there is increased recognition that the way people accumulate

time in these domains is also important. The guidelines of American College of Sports and Medicine suggest that physical activity be accumulated in bouts of ≥ 10 minutes duration (54). For sedentary behaviour, it has been shown that regularly breaking up time spent in sedentary behaviour, with light intensity activity every 30 minutes, has been beneficially associated with lower waist circumference, body-mass index , level of triglycerides and fasting 2-h plasma glucose level (71). To date, information on the way people with COPD accumulate time in both physical activity and sedentary behaviour is limited, and there are no data on this in a Saudi population. This lack of information limits the ability to design interventions to optimise performance of physical activity and sedentary behaviour for people with COPD.

To date, studies that have measured the level of physical activity in Saudi population used questionnaires such as the international physical activity questionnaire (72-74). However, quantifying physical activity (or sedentary behaviour) using subjective measures (e.g., diary and questionnaires) has been shown to be inaccurate, particularly in older people, when compared with objective measures (e.g., pedometers or accelerometers) (75). Information on sedentary behaviour and physical activity in Saudi nationals with COPD obtained using robust objective methods has not been reported.

1.4.2.1 Significance and novelty of the research

Several studies have explored the physical activity levels of people with COPD and compared these data with that collected in healthy controls. These studies were conducted in Belgium, Brazil, Sweden, Japan, Spain, Romania and the United Kingdom (56, 57, 76-80). Although people with COPD are characterised by low levels of physical activity, these low levels are different between people from different countries (81). Pitta et al (81) demonstrated that, after adjusted for confounders such as age and disease severity, people with COPD from Brazil had higher levels of physical activity compared with matched people with COPD from Austria. Therefore, data from other countries may not be representative of Saudis with COPD. The findings of this research will be the first to report data on physical activity and sedentary behaviour as well as data on the pattern of accumulation of physical activity and sedentary behaviour in Arabic countries, specifically in Saudi

Arabia. Obtaining data on sedentary behaviour and physical activity of Saudi nationals with COPD and comparing these data with that collected in healthy people of a similar age and gender will be important to assist health professionals in Arabic Gulf countries, especially in Saudi Arabia, to understand the lifestyle adopted by their patients. The findings of this study will also help health professionals to provide physical activity and sedentary behaviour goals to their patients, aimed at optimising health outcomes in this population. Further, the results of this study have the potential to stimulate research in Arabic Gulf countries investigating strategies aimed at changing barriers to physical activity such as fear of embarrassment when undertaking exercise (73).

1.5 Research Aim 4

To report associations between the quality and emotional components of the D-12 with physical activity and sedentary behaviour in people with COPD.

1.5.1 Research hypothesis

The hypothesis was that the quality and emotional response components of the D-12 will associate with the time spent in walking based activity and sedentary behaviour in people with COPD.

1.5.2 Background

It is generally accepted that people with COPD limit their participation in physical activity and become more sedentary to minimise their experience of dyspnoea (10, 57). Several studies have explored the associations between objectively measured physical activity and dyspnoea in people with COPD (57, 82-85) with most reporting significant associations that range between r = 0.15 to r = 0.57 (82, 84-86). For example, Watz et al (85) measured physical activity, using an accelerometer, of 163 people with mild to very severe stable COPD. The authors demonstrated a moderate association between daily steps and functional limitation resulting from dyspnoea, using the Medical Research Council dyspnoea scale, ($r = -0.57$, $p < 0.001$), indicating that greater limitations due to dyspnoea impacts negatively on participating in daily physical activity in COPD (85). To date, no study has reported an association between dyspnoea and sedentary behaviour in people with COPD. In addition,

determining whether the quality of dyspnoea and/or the emotional response to dyspnoea has the most impact on sedentary behaviour and physical activity of people with COPD has not been explored.

1.5.2.1 Significance and novelty of the research

The findings of this study will extend the results of the first study in this program of research by providing further evidence of the validity of the D-12. To date, no research has identified whether it is the quality or the emotional response components of dyspnoea that impacts most on sedentary behaviour or physical activity levels. Therefore, the results of this research will demonstrate which specific components of dyspnoea have the greatest impact on sedentary behaviour and physical activity. The findings of this study may promote future research into ameliorating the appropriate component of dyspnoea, either the quality of the sensation or the emotional response to it, which seems to have the greatest adverse effect on participation in physical activity and the accumulation of time spent in sedentary behaviour. In turn, this may assist in reducing the time spent in sedentary behaviour and increasing the time spent participating in physical activity in people with COPD with the overall aim of improving health outcomes.

1.6 Study location

All studies were undertaken in Riyadh, the capital city of Saudi Arabia, at King Fahad Medical City. The estimated population of Riyadh is 4,506,321 (87). King Fahad Medical City is a public and a tertiary care referral centre. In addition, it is considered the largest and most advanced medical facility in the Middle East (88). It comprises four hospitals, main hospital, maternity hospital, pediatric hospital, and rehabilitation hospital, making up a total of 1,200 beds. King Fahad Medical City provides high quality of services similar to those provided in Western countries such as the United States of America. More than 19,171 inpatients annually and over 238,404 outpatients are treated at King Fahad medical city. Respiratory care at King Fahad Medical City is provided by highly trained consultants, residents and nursing technicians for inpatient and outpatient departments.

CHAPTER 2

LITERATURE REVIEW

2.1 Overview

This literature review is divided into four parts. Part 1 (Section 2.2) is an overview of chronic obstructive pulmonary disease (COPD) and includes information pertaining to its causes and risk factors and the prevalence of COPD. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification for disease severity, as well as the impact and costs associated with COPD are also discussed in part 1. Part 2 (Section 2.3) provides information related to dyspnoea in people with COPD. In addition, the relationships between dyspnoea and clinical outcomes, as well as tools that are used to measure dyspnoea in people with COPD are discussed. Interventions to reduce dyspnoea in COPD are also described. Part 3 (Section 2.4) provides a definition for an acute exacerbation of COPD (AECOPD) and information related to the causes of an AECOPD. The effects of an AECOPD on clinical outcomes and the economic burden of an AECOPD are also discussed. In addition, information about the management of an AECOPD is described. Part 4 (Section 2.5) reviews the literature pertaining to physical activity and sedentary behaviour and public recommendations on physical activity levels for health. The various methods used to measured physical activity and factors that are associated with the measurement of physical activity and sedentary behaviour in people with COPD are discussed in part 4.

Part 1

2.2 Introduction

Chronic obstructive pulmonary disease is a preventable and treatable disease characterised by expiratory airflow limitation that is not fully reversible (10). The airflow limitation is usually progressive and arises as a consequence of an abnormal inflammatory response to noxious particles or gases in the lungs (10). This disease is caused by a combination of small airways disease (bronchiolitis) and destruction of the lung parenchyma (emphysema). The relative contribution of these two pathological abnormalities varies between people. Chronic inflammation causes structural changes in the airway walls, resulting in narrowing of the airway lumen. The inflammation and structural changes in the peripheral airways leads to a decrease in the volume of air exhaled during the first second of a forced expiration (FEV_1) (10). Destruction of the lung parenchyma results in a loss of the alveolar attachments to the respiratory bronchioles and a decrease in lung elasticity (89). In turn, these changes contribute to expiratory airflow limitation and abnormalities of gas exchange (89). Abnormalities in gas exchange lead to hypoxemia (low levels of oxygen in the blood) and hypercapnia (high levels of carbon dioxide in the blood) and have several mechanisms in COPD. Gas transfer for oxygen and carbon dioxide reduces when the disease progresses (89). Reduction in the ventilation may also be due to reduced ventilation drive. This reduction may lead to carbon dioxide retention when it is coupled with decreased ventilation because of a high work of breathing due to severe obstruction and hyperinflation combined with ventilatory muscle impairment (90). The abnormalities in alveolar ventilation and a decreased pulmonary vascular bed lead to further worsen ventilation-perfusion abnormalities (89). The presence of expiratory airflow limitation and its severity can be confirmed by spirometry, which provides a reliable and objective measurement of static lung function (10).

The characteristic of respiratory symptoms of COPD are both chronic and progressive dyspnoea, cough and sputum production (10). An acute deterioration in the respiratory symptoms of people with COPD is known as an AECOPD (10) (Section 2.4). The frequency of an AECOPD is often increased with increasing

disease severity (91). An AECOPD is also associated with accelerated decline in lung function and health-related to quality of life (HRQoL) (92) (Section 2.4).

2.2.1 Causes and risk factors of COPD

Environmental exposure to noxious gases and genetic abnormalities are two well-known risk factors in the development of COPD (10). Exposure to tobacco smoke is considered the major environmental risk factor for COPD (10). Other important environmental risk factors are indoor air pollution (e.g. biomass fuels used for cooking), outdoor air pollution, respiratory infections and occupational exposure to organic and inorganic dusts, fumes and chemicals (10, 93, 94). However, only 15% to 20% of smokers develop clinically significant airflow limitation (95), suggesting that genetic factors also play a role in the development of the disease. The well-documented genetic risk factor for COPD is alpha-1 antitrypsin deficiency (10, 96). Other candidate genes have also been suggested in the pathogenesis of COPD, but these genes have not yet been identified (10).

2.2.2 Prevalence of smoking

The prevalence of smoking varies widely across the world (97). For example, the Burden of Obstructive Lung Disease (BOLD) study showed that the prevalence of smoking is as high as 50% in Adana city in Turkey and as low as at 14% in Sydney, Australia (97). In Arabic Gulf countries, the most common forms of smoking are cigarette smoking and shisha smoking (waterpipe) (98). The shisha is a device that heats tobacco by charcoal, filters the resulting smoke into a bowl of water and then passes it to a rubber pipe for inhalation through the mouth (99). This form of smoking is considered a social and popular behaviour in Arabic cultures (100). However, shisha smoking has been found to be associated with deleterious health effects such as lung cancer, respiratory illness and periodontal disease (101). The prevalence of shisha smoking in Arabic Gulf countries ranges from 9% in Oman to 12% in Kuwait (11, 98, 102-104).

The prevalence of smoking (cigarettes or shisha or both) differs among Arab Gulf countries (11, 102-104). In general, the overall smoking prevalence in the Saudi population aged ≥ 40 years is 28%, with a rate of 39% in males and 7% in females (11). The prevalence of smoking in the Saudi population is lower than that reported

in Qatar (37%), with a rate of 42% in males and 7% in females, aged ≥ 15 years (102). In the United Arab Emirates, the prevalence of smoking in adults aged ≥ 18 years is 24% in males and 1% in females (overall rate of smoking was not reported in this study) (103). In contrast, Oman appears to have the lowest prevalence of smoking (7%) in adults aged ≥ 20 years, with a rate of 13% in males and 0.5% in females compared to the aforementioned Arabic Gulf countries (104). The differences in the prevalence of smoking between Arabic Gulf countries reported in this literature could be explained in part by different sample sizes and different ages included in the studies.

2.2.3 Prevalence of COPD

The prevalence of COPD varies considerably throughout the world (97). The variations in reported prevalence refer to several factors such as the diagnostic criteria of COPD used, the study design, the study population, proportions of age and gender, and the response rate. Published epidemiological studies of COPD prevalence defined COPD using either post-bronchodilator spirometry or a questionnaire based definition of COPD (1, 2, 4, 6, 8, 9, 105, 106). Using post-bronchodilator spirometry for a diagnostic of COPD is a reliable and objective measurement of static lung function (10). However, using this method in epidemiological studies has some disadvantages that introduce the possibility of selection bias affecting the prevalence estimates (8). These disadvantages include poor response rate, and it may be difficult to apply in very large populations as it requires medical professionals to conduct the test and interpret data obtained, and may only include people seeking medical care. The questionnaire based definition of COPD is easy to apply in large populations. However, respondents to the questionnaire may not recognise the symptoms of COPD, which definitely result in the underestimation of the prevalence of COPD. Furthermore, COPD is not necessarily diagnosed until it is moderately advanced.

Only three studies in the Arab Gulf countries have reported the prevalence of COPD diagnosed using post-bronchodilator spirometry, two of them were in Saudi Arabia and one was in the United Arab Emirates (2, 105, 107). In Saudi Arabia, the BOLD study was conducted in Riyadh city and recruited 784 people (361 females, 46% of the total) aged ≥ 40 years by stratified multistage random sampling. All participants

performed post-bronchodilator spirometry and completed questionnaires related to respiratory symptoms and cigarette smoking history (105). The overall prevalence of COPD was 4.2%, being higher in males (5.7%) than females (2.5%), the classification of COPD severity was not reported.

Compared to the international BOLD studies, defined by spirometric criteria among people aged ≥ 40 years, the prevalence of COPD in Saudi Arabia is lower than that reported in many countries: 26.1% in Austria (4), 24% in the Netherlands (5), 20.8% in the Philippines (6), 18% in Iceland (108), 16.2% in Sweden (7), 13.2% in Germany (109), 8.2% in China (9), and 7.9% in Australia (8). Among 11 international sites, the international BOLD reported the prevalence of COPD in males and females, defined by spirometric criteria (97). The prevalence of COPD in people aged ≥ 40 years ranged from 8.5% in Reykjavik, Iceland, to 22.2% in Cape Town, South Africa, in males; and from 3.7% in Hannover, Germany, to 16.7% in Cape Town in females (97). The prevalence rates of COPD in Saudi males and females lie at the lower end of the international range for males and females. It should be noted that the BOLD study was limited to one city in Saudi Arabia and may not represent the prevalence rate of COPD in the general population.

Another Saudi study was conducted in the three largest cities, namely, Riyadh, Jeddah and Dammam. The sample comprised 501 smokers (52 females, 10% of the total) with a smoking history ≥ one year and aged ≥ 40 years who were attending private healthcare clinics. All participants performed post-bronchodilator spirometry and completed a questionnaire related to information on smoking history and respiratory symptoms (2). The findings showed that 14% (68 males and three females) had COPD and, of these, 56% had moderate COPD and 44% had severe COPD (2). However, this study selected a specific population seeking health provider advice at primary healthcare clinics which does not show a true picture of prevalence of COPD in the general population. Moreover, including only smokers in this study are likely to overestimate the prevalence of COPD in the population, where smoking is the primary risk factor for the development of COPD.

In Abu Dhabi in the United Arab Emirates, the prevalence of COPD was explored in 520 people (234 females,45% of the total) aged between 40 and 80 years who were selected from the catchment population of a military hospital and recruited by

random phone calls. All participants performed post-bronchodilator spirometry and completed questionnaires related to information about their smoking history and bakhour and biomass exposure (107). The prevalence of COPD was 4% and, of these, 5% had mild COPD, 63% had moderate COPD and 32% had very severe COPD (107). However, the majority of participants in this study were non-smokers (70%), who are unlikely to have COPD. In addition, there was no difference in prevalence between males and females (107). This study only included participants from one area in one city, and therefore, it may not represent the prevalence of COPD in Abu Dhabi as a whole. Including a large sample from the community is needed in order to represent the prevalence of COPD in a population.

A survey study, named the BREATH study, conducted in the Middle East and North Africa region reported that the prevalence of COPD in Saudi Arabia (n = 9,730, 35% females) was somewhat similar to that found in the United Arab Emirates (n = 3,494, 48% females) was 2.4% and 1.9%, respectively, in people aged ≥ 40 years (1). The study showed that COPD was more frequent in males than females, 3.5% versus 1.0% in Saudi Arabia and 2.6% versus 0.4% in the United Arab Emirates. The definition of COPD in the survey study was based on two criteria. First, either a diagnosis of COPD, emphysema or chronic bronchitis OR the presence of cough with sputum, breathlessness or symptoms comparable with chronic bronchitis. The second criterion was related to smoking exposure of ≥10 years. Compared to data obtained from the Confronting COPD International Survey study (106) that used a comparable methodology and the same COPD definition as that used in the BREATHE study, the prevalence of COPD in Saudi Arabia and the United Arab Emirates are lower than that from many countries: 12.0% in Brazil, 9.0% in Germany and in Mexico, 8% in the United of Kingdom, 7% in the United States of America and in Japan. The definition of COPD used in the survey studies could underestimate the prevalence of COPD as people may not be able to recognise COPD symptoms. In addition, the prevalence of tuberculosis is high in developing countries and that may cause chronic irreversible airflow obstruction which may pose a problem regarding the definition used for COPD. Furthermore, the diagnosis of COPD should be made on the basis of measuring lung functions using post-bronchodilator spirometry (10), which was not used in the survey studies.

Data on the prevalence of COPD in the Arab Gulf countries are virtually absent, or if available are often limited to one city or based on inadequate definitions. Therefore, studies aim to determine precise estimates of the prevalence and the burden of COPD in the Arab Gulf countries need to conduct post-bronchodilator spirometry and use validated questionnaires.

2.2.4 Cost of COPD

Chronic obstructive pulmonary disease places a significant burden on healthcare resources (110). The direct costs of COPD in the United States of America have been estimated to be $15.7 billion USD per year (111). This high cost is largely accounted for by hospital admissions and the healthcare management of the disease including outpatient clinic appointments and medications (112). Equivalent data for costs are not available for any of the Arabic Gulf countries.

The direct cost alone does not reflect the full burden of COPD on people and society. Indirect costs account for a significant proportion of the burden of the disease. These indirect costs associated with COPD include loss of productivity and impaired work performance, lost income due to premature retirement, absenteeism, disability and activity limitation (113). The ability to work has been shown to decrease as disease severity increases (113). It has been shown that family caregivers of people with advanced COPD experience poor psychological well-being compared to those carers of people with early stage COPD (114).

2.2.5 Classification of disease severity

A possible diagnosis of COPD should be considered for an individual (i) aged ≥ 40 years, (ii) who reports dyspnoea, chronic cough or sputum production, and/or (iii) a history for exposure to risk factors for the disease, such as tobacco smoke or occupational dusts, for ≥10 years (10). Post-bronchodilator spirometry is essential for the diagnosis of COPD and assessment of disease severity. A post-bronchodilator ratio of FEV_1/forced vital capacity (FVC) < 0.70 confirms the presence of irreversible airflow limitation and therefore of COPD (10). The severity of COPD is classified based on the measurement of post-bronchodilator FEV_1 expressed as a percentage of the predicted value in healthy people. The most widely recognised

system for classifying severity is the GOLD, which classifies the severity of COPD into four grades (1, 2, 3 and 4) as shown in Table 2-1 (10).

Table 2-1: Classification of the severity of COPD as defined by the Global Initiative for Chronic Obstructive Lung Disease (10).

Grades	In people with $FEV_1/FVC < 0.70$	
1	Mild	$FEV_1 \geq 80\%$ predicted
2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
4	Very severe	$FEV_1 < 30\%$ predicted

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity

2.2.6 Impact of COPD

Chronic obstructive pulmonary disease not only affects the lungs, but is also characterised by extrapulmonary effects such as cardiovascular disorders and skeletal muscle dysfunction (115, 116). The main symptoms experienced by people with COPD are exertional dyspnoea and fatigue (117). Poor HRQoL, feelings of anxiety and depression, decreased exercise capacity and physical activity are prevalent in people with COPD (56, 118, 119). Muscle weakness in the lower extremities is also considered to be a major problem in people with COPD, influencing exercise capacity (120). There is also increasing recognition of the importance of comorbidities in people with COPD (121). The following paragraphs describe the symptoms that include dyspnoea and fatigue, a reduction in exercise capacity and physical activity, poor HRQoL, feelings of anxiety and depression, and systemic manifestations and/or comorbidities in people with COPD.

Dyspnoea is the most distressing symptom experienced by people with COPD and is frequently the main reason for seeking medical assistance (24). In people with COPD, expiratory flow limitation leads to an increase in the volume of air in the lungs at the end of spontaneous expiration, known as pulmonary hyperinflation (122). In most people with COPD, hyperinflation increases the ventilatory demand during exercise or physical activity as well as when airflow limitation increases during an AECOPD (24, 37, 123). More details on dyspnoea are provided in Section 2.3.

Fatigue is considered another prominent symptom experienced by people with COPD (124). An increase in the work of breathing and dyspnoea severity has been reported to lead to deconditioning of muscles and fatigue in those with COPD (125). Fatigue in general has been shown to be a strong predictor for the risk of hospitalisation, independent of COPD severity (126). During a 20 month follow-up period, the length of hospital stay of 83 people with mild to very severe COPD (aged 72 ± 9 years) was demonstrated to increase by a factor of four for every unit increase in fatigue experienced, evaluated using an Identity-Consequences Fatigue Scale (126). Both dyspnoea and leg fatigue lead to the avoidance of physical activity, which ultimately results in functional limitation and impaired HRQoL (117, 127).

Impaired exercise capacity is a prominent feature of people with COPD (128). Compared with reference values and/or data reported in healthy people, a decline in exercise capacity, measured as a reduced distance walked during field walking tests (56, 57) or maximum work rate achieved during cycle ergometry testing (34, 129), has been demonstrated in people with COPD. Longitudinal data showed that the decline in exercise capacity occurs independent of the change in airflow limitation in those with severe COPD (130). In addition, exercise capacity is a stronger predictor of mortality than FEV_1 (130, 131). This is likely to be because exercise capacity is influenced by skeletal muscle dysfunction and pulmonary impairment, thereby, reflecting the primary pulmonary and secondary systemic manifestations of COPD (132).

Research on the physical activity levels of people with COPD has consistently demonstrated that this population have a lower level of physical activity compared to their healthy peers (56-58). Furthermore, a decline in physical activity levels was found to be related to an increased risk of hospitalisation and mortality, and decreased HRQoL (133, 134). More details on physical activity in people with COPD are provided in Section 2.5.

Health-related quality of life is a multidimensional construct that reflects physical, psychological and social function as well as well-being (135). Chronic obstructive pulmonary disease places a significant burden on people by affecting the physical, psychological and social components of HRQoL and well-being (136, 137). People with COPD have been found to have impaired HRQoL compared to healthy people and others with chronic conditions such as prostate cancer, hyperlipidaemia and diabetes mellitus (138, 139). The magnitude of this impairment in HRQoL has a moderate to stronger association (r ranging from 0.40 to 0.70, all $p < 0.001$) with dyspnoea and decreased exercise capacity (135, 140).

Feelings of anxiety and depression are common among people with COPD, with the prevalence rate ranging from 10% to 96% depending on the criteria used to define them (141). Feelings of anxiety and depression are often associated with increased disability and morbidity (142), and have a negative impact on the HRQoL of those with COPD (143, 144).

As mentioned earlier, COPD not only impacts on lungs, but has other consequences, which might be considered systemic manifestations and/or comorbid conditions. In people with COPD, loss of skeletal muscle mass and strength, in particular of the quadriceps muscles has been demonstrated (145, 146). This muscle atrophy is due to several factors that include chronic inflammation, malnutrition, arterial blood gas abnormalities, electrolyte imbalance, low physical activity, the side effects of medications such as statins, and compromised oxygen delivery due to right heart dysfunction (145). One of the main muscles used for ambulation is the quadriceps muscle and a significant reduction in quadriceps endurance has been demonstrated in people with COPD (147, 148). Computed tomography scans of the thigh muscles demonstrated that people with COPD had a reduction in skeletal muscle mass when compared with healthy people (149). Muscle weakness and leg fatigue have a negative impact on exercise tolerance, as it has been shown that people with COPD who had weaker muscles reported more leg fatigue and showed decreased peak exercise capacity than those with less weak muscles (150).

In people with COPD, changes in the morphology of the quadriceps muscle have been demonstrated (151, 152). Compared with age-matched healthy people, the vastus lateralis muscle of people with COPD has a lower propotion of Type I fibers and a higher proportion of Type IIa and Type IIb fibers (151, 152). In addition, a decrease in cross sectional area across Type I, IIa and IIab fiber types has also been found in people with COPD compared to age-matched healthy people. Changes in muscle biochemistry have been demonstrated in people with COPD when compared to age-matched normal people (153). These changes include reductions in the activity of two oxidative enzymes that play a part in aerobic metabolism; citrate synthase and 3-hydroxyacyl CoA dehydrogenase (153). A decrease in the activity of citrate synthase, but not 3-hydroxyacyl CoA dehydrogenase, has been found to be associated with more profound impairments in aerobic capacity (153).

The most frequently reported systemic manifestations or comorbidities in COPD include cardiovascular diseases, musculoskeletal conditions, psychological disorders, metabolic syndrome, osteoporosis and lung cancer (154). These comorbidities increase the risk for hospitalisation and have a major impact on HRQoL, survival and

health care costs associated with COPD (155-157). In addition, comorbid conditions can occur at any severity grade of COPD (157, 158).

In summary, COPD results in symptoms that include dyspnoea and fatigue, poor HRQoL, a decline in exercise capacity and physical activity, feelings of anxiety and depression, and is associated with systemic manifestations and/or comorbidities. The burden of these symptoms and associated conditions can been seen in the daily lives of those with COPD.

Part 2

This part provides information related to dyspnoea in people with COPD. In addition, the relationships between dyspnoea and clinical outcomes, as well as tools that are used to measure dyspnoea in people with COPD are discussed. Interventions to reduce dyspnoea in COPD are also described.

2.3 Dyspnoea in COPD

The American Thoracic Society defines dyspnoea as a subjective experience of breathing discomfort comprising distinct sensations that vary in quality and intensity (13). These sensations arise from interactions between multiple physiological, psychological, social and environmental factors (13). Dyspnoea is often an indication of serious disease, and it can be extremely unpleasant and frightening for people with COPD (159). Dyspnoea can be severely debilitating for those with COPD (160) and is often the primary reason for seeking medical attention (25).

2.3.1 Pathophysiology of dyspnoea and neuromechanical disassociation

In the COPD population, factors that increase the demand on the ventilatory system are likely to lead to dyspnoea when ventilatory capacity is not adequate to meet increased ventilatory demands (161). Neuromechanical imbalance is a popular idea to explain the contribution of the respiratory muscles to the development of dyspnoea (13). This theory suggests that dyspnoea results from a disequilibrium between the respiratory motor command and the resulting afferent feedback from proprioceptive and other sensory receptors. Therefore, when the afferent feedback from the chest wall relating to intrathoracic pressure changes, respiratory muscle length and

movement of the lungs are interpreted as insufficient corresponding motor command, it gives rise to dyspnoea (161, 162). Thus, the disparity between the motor command from the central nervous system to breathe, and the inefficient mechanical response of the respiratory system results in dyspnoea in people with COPD (162).

Although several factors have been implicated in reducing the capacity of the respiratory muscles to meet the increase in the ventilatory demands associated with exercise, the following sections will focus on the most important factors which are pulmonary hyperinflation, mechanical loads on the inspiratory system and gas exchange abnormalities in people with COPD.

2.3.1.1 Pulmonary hyperinflation

Pulmonary hyperinflation is one of the major contributory factors to dyspnoea in COPD (163). In COPD, the combined effects of peripheral airway narrowing and reduced elastic recoil of the lung lead to an abnormal increase in the volume of air remaining in the lungs at the end of spontaneous expiration, termed pulmonary hyperinflation (122). These changes decrease the ability of the ventilatory system to accommodate increased respiratory demands (i.e. during exercise, an AECOPD), by increasing tidal volume. Consequently, a decrease in the time available for expiration occurs as respiratory rate increases, leading to further increased trapped gas in people with COPD (164). The worsening hyperinflation increases the overall dimensions of the rib cage, causing the inspiratory muscles to produce more tension to bring about the same pleural pressure changes to achieve the same tidal volume (165). Hyperinflation also results in shortening of the inspiratory muscles although sarcomere adaption does take place in setting of chronic hyperinflation (166).

In addition to the effects that pulmonary hyperinflation has on COPD, it may also contribute to dyspnoea through other mechanisms. Acute dynamic pulmonary hyperinflation may cause a rapid rise in the intrathoracic pericardial pressure which can then mechanically compress the intra-alveolar vessels (167). This leads to worsening hypoxia and increased pulmonary arterial resistance and pressure causing severe dyspnoea (167).

2.3.1.2 Mechanical loads on the inspiratory system

Various types of mechanical loads (i.e. elastic, threshold, resistive) on the respiratory system also contribute to the sensation of dyspnoea in people with COPD. Due to the loss of elastic recoil, the chest wall and lungs become stiff, imposing additional muscle load (168). Muscle loads that are imposed by stiffness of the chest wall and lungs which needs to be overcome by the inspiratory muscles to produce increased negative pleural pressures during inspiration, are known as elastic loads (162).

The threshold load refers to the increased intra-alveolar pressure in the hyperinflated COPD lungs at the end of each expiration (169, 170). It is also called as the intrinsic positive end expiratory pressure (170). This increased pressure has to be overcome in the next inspiration, therefore requiring more effort by the inspiratory muscles (169).

The third type of the mechanical load is a resistive load which is imposed by the narrowed airways (171). In COPD, due to permanent destruction of the alveolar air sacs, excessive mucus impaction in the bronchial lumen and fibrosis of airways there is fixed obstruction to the airflow resulting in a resistive load (10).

2.3.1.3 Gas exchange abnormalities

Gas exchange abnormalities occurring as result of ventilation/perfusion mismatch can contribute to the development of dyspnoea (172). An acute increase in carbon dioxide levels the arterial blood provokes a chemoreceptor-driven increase in inspiratory motor command, which leads to an in increase dyspnoea, in people with COPD (173). Chronic carbon dioxide retention contributes to increased dyspnoea during daily activities (10). In COPD, carbon dioxide retention has been associated with increased inspiratory muscle weakness (174). It is likely that the cause of increased carbon dioxide levels in the arterial blood of people with weak inspiratory muscles results from the gradual deterioration in the mechanical properties of the lung and inspiratory muscle function, which leads to a relatively high force required for each breath and the subsequent development of a rapid breathing pattern (175). Such a breathing pattern decreases inspiratory muscle fatigue and minimises inspiratory muscle effort and dyspnoea, but at the expense of alveolar ventilation (176, 177). Dyspnoea reported by people with chronic carbon dioxide retention is

more likely to result from neuromechanical disassociation because of the imbalance between the load and the capacity of the inspiratory muscles (13).

Hypoxia increases the reliance on anaerobic energy systems with consequent lactate production triggering increased ventilation, contributing to dyspnoea (178). Supporting the hypothesis of these physiological changes is the finding that delivering oxygen to those with COPD during exercise decreases lactate concentration and ventilation, which in turn, contributes to reduced dyspnoea (178).

In summary, the pathophysiology of dyspnoea that arises in COPD due to inspiratory muscles dysfunction, pulmonary hyperinflation, and increased mechanical loads on the inspiratory system and gas exchange abnormalities.

2.3.2 Relationship between dyspnoea and clinical outcomes

In people with COPD, dyspnoea is considered one of the major symptoms that has a relationship with important clinical outcomes such as exercise capacity, HRQoL, feelings of anxiety and depression, lung function and mortality.

2.3.2.1 Exercise capacity

Dyspnoea is one of the one of symptoms that limits exercise in the majority of people with COPD and can lead to avoidance of activity with consequent skeletal muscle deconditioning (37, 167, 179). Although dyspnoea is the main symptom that limits the performance of people with COPD during walking-based tests, dyspnoea has also been reported in conjunction with fatigue as limiting exercise tolerance during cycle ergometry testing (180). In people with COPD, a moderate to strong association has been demonstrated between dyspnoea and functional exercise capacity, measured by a six-minute walk distance (6MWD) ($r > 0.4$, $p < 0.05$) (23, 181). This association indicates that as dyspnoea severity increases, functional exercise capacity declines in people with COPD.

2.3.2.2 Health-related quality of life

In people with COPD, dyspnoea is associated with poor HRQoL (14, 140). Studies have explored the relationship between functional limitation due to dyspnoea, using the Medical Research Council (MRC) dyspnoea scale, a 5-point ordainal scale, and

disease specific HRQoL questionnaires such as the St. George's Respiratory Questionnaire (SGRQ) (182, 183). These studies demonstrated that greater impairments in the HRQoL of people with COPD were found in those who had a high grade of functional limitation resulting in dyspnoea of a MRC grade 4 or 5, ($p < 0.05$) (182, 183).

In general, dyspnoea is often one of the determinants of HRQoL, and has significant moderate to strong associations ($r \geq 0.5$) with the impairments in HRQoL in people with COPD (182). In addition, significant moderate to strong (≥ 0.4) associations have been found between dyspnoea and generic measures of HRQoL, such as the Medical Outcomes Study Short Form 36-item questionnaire, in people with COPD (184, 185)

2.3.2.3 Feelings of anxiety and depression

Feelings of anxiety and depression are commonly experienced by people with COPD (10, 186). Several studies have explored the associations between dyspnoea or a functional limitation resulting from dyspnoea, and feelings of anxiety and depression (187-189). These studies found that greater dyspnoea was observed in those who had reported higher anxiety and depression scores on screening instruments (187-189). For example, in 29 people with moderate to severe stable COPD, Borges et al (190) assessed the relationship between feelings of anxiety and depression, measured using the Hospital Anxiety and Depression Scale (HADS), with a functional limitation resulting from dyspnoea, measured using MRC dyspnoea scale. The authors demonstrated that compared to those without feelings of anxiety or depression, people with greater feelings of anxiety (HADS score > 8) had reported 29% increase in their MRC scores, while those with greater feelings depression (HADS score > 9) had reported 30% increase in their MRC scores

2.3.2.4 Lung function

The FEV_1 is used to determine the severity of COPD, expressed as a percentage of the predicted value in healthy people (10). In people with COPD, a weak association has been demonstrated between FEV_1 and dyspnoea measures (23, 191-194). Therefore, FEV_1 may not reflect the severity of dyspnoea in COPD as it has been demonstrated that changes in FEV_1 were not associated with change in dyspnoea

during exercise (r = 0.07, $p = 0.8$) in people receiving short-acting bronchodilators (195). In COPD, it has been shown that indices related to pulmonary hyperinflation, such as inspiratory capacity, are more closely related to dyspnoea than FEV_1 (196, 197). After receiving a short-acting anticholinergic bronchodilator, an improved inspiratory capacity of 14% predicted has been shown to be associated with improvement in dyspnoea (11% reduction in Borg dyspnoea ratings, $p < 0.05$), during exercise (198).

2.3.2.5 Mortality

Dyspnoea appears to be a predictor of mortality in people with COPD. Nishimura et al (26) included a total of 227 people with COPD (FEV_1% predicted = 41 ± 17) who were followed for five years and found that the relative risk of mortality increased with increasing dyspnoea level, measured using the MRC dyspnoea scale. Specifically, the authors showed that the relative risk of mortality, in comparison to those with MRC grade 2, was 2.21 (95% confidence interval [CI] 1 to 5) for people with grade 3, 8.3 (95% CI 3 to 20) for people with grade 4, and 61.3 (95% CI 13 to 285) for people with grade 5 (26). Similarly, a recent study showed that, over five years, the survival rate of people with COPD increased with decreased level of dyspnoea, assessed using the modified MRC (mMRC) (199). The study found that those who had a lower grade of dyspnoea (mMRC ≤ 1) had a five-year survival of 76%, whereas for those who had a higher grade of dyspnoea (mMRC ≥ 2) the survival at five years was 56% (199).

In summary, dyspnoea in people with COPD is associated with reduced functional exercise capacity and HRQoL, feelings of anxiety and depression and reduced lung function and increased mortality.

2.3.3 Measurement of dyspnoea

The purposes of measuring dyspnoea are: to discriminate between people who have less dyspnoea and those who have more dyspnoea, to titrate exercise intensity and to determine whether dyspnoea has changed over time and/or as a result of treatment (evaluation). Numerous tools are available for measuring dyspnoea which can be classified as unidimensional and multidimensional tools. The use of unidimensional tools is often preferred when measuring general severity of dyspnoea sensation either

averaged over a period of time or at a point in time, for example before, during, and after exercise (160, 200). Although the unidimensional tools are self-administered and take only a few moments to complete, it is not appropriate to be used in illiterate people. The unidimensional tools do not provide information pertaining to components of dyspnoea such as the quality and emotional response to dyspnoea sensation.

The multidimensional tools provide information related the effect of dyspnoea across multiple domains, such as daily activities and/or emotional and mental functioning. In addition, it is often preferred to be used when comparing the impact of dyspnoea on multiple domains between different populations. The multidimensional tools are available either self-administered and/or interviewer-administered. Compared to the unidimensional tools, the multidimensional tools are lengthy and require more time to complete.

It is important to note that none of the tools can be considered as a 'gold standard' demonstrating accurate, comprehensive assessment of dyspnoea in all settings (201). Therefore, selecting the most appropriate tool depends on the context and purpose of measurement. The following section presents and discusses common tools used to measure dyspnoea in people with COPD.

2.3.3.1 Unidimensional tools

The two unidimensional tools that are commonly used to quantify dyspnoea are the modified Borg scale (17) and the visual analogue scale (VAS) (18, 202). The Borg scale and the VAS are most often used to measure an individual's perceived dyspnoea severity during exercise testing (160). The oxygen cost diagram (OCD) and the MRC dyspnoea scale are other unidimensional tools that are used to measure dyspnoea in people with COPD.

2.3.3.1.1 Modified Borg scale

The modified Borg scale is a 0 to10 categorical scale with descriptors linked to specific numbers with ratio properties (17). This scale was originally designed to measure perceived exertion during activity and was scored from 6 to 20 (corresponding to a heart rate range of 60 to 200 beats per minute). Later, the scale

was modified to a 0 to 10 point scale to quantify the intensity of dyspnoea (17); this format of the scale is the one most widely used (203).

The modified Borg scale is considered to be a ratio scale in whereby a rating of '4' shows that dyspnoea is twice as severe as a rating of '2', '8' is twice as severe as '4', and so on (16). In people with COPD, the modified Borg scale has been shown to be reliable, with coefficients of variation for the maximal Borg score and Borg score at two minutes of cycle exercise were 3 ± 1% and 3 ± 2% respectively (204). The Borg scale has also been demonstrated as valid, as shown by a strong association between the score of Borg scale with both minute ventilation and oxygen consumption ($r > 0.92$, $p < 0.01$) in people with COPD during exercise (204). Besides being reliable and valid, the scores obtained using the Borg scale have been shown to change following an intervention such as pulmonary rehabilitation in COPD (46, 205), with a large effect size > 0.90 (206).

2.3.3.1.2 Visual Analogue Scale

The VAS consists of either a horizontal or a vertical line, usually 100 mm in length, with clear anchors defined at each end of the scale, using words such as 'not breathless at all' to 'extremely breathless', or 'not breathless' to 'breathlessness as bad as it can be' (18). The individual places a line between the anchor points to indicate his or her dyspnoea level, and the distance from the left side or bottom of the VAS is measured (18). The VAS has been shown to be reliable, with a coefficient of variation of 6% seen during exercise tests performed two weeks apart in people with COPD (207). In people with COPD, the VAS has been shown to be valid, by demonstration of a strong association between the scores of the VAS with the Borg scale ($r = 0.99$, $p < 0.01$) (208). The VAS has been shown to change in response to an intervention, such as pulmonary rehabilitation or supplemental oxygen (209-211), and yielded a moderate to large effect size ranging from 0.48 to 1.26 (206).

Although the VAS is easy to use, comparison between studies is difficult because of the use of the VAS to measure different aspects of dyspnoea, such as 'uncomfortable breathing', 'distress due to breathlessness' or 'bother caused by breathlessness' (16). Consistent phrasing of the question is essential because the wording may affect an instrument's psychometric properties For example, Wilcock et al (212) revealed that

questions about ‘worst breathlessness over the past 24 hours’ (from ‘not breathless at all’ to ‘breathlessness as bad as you can imagine’) was associated with lower standard deviation (SD) of the difference between the two tests, one to eight days apart, when compared with questions related to breathlessness ‘right now’, ‘average breathlessness over the past 24 hours’ and ‘bother caused by breathlessness over the past 24 hours’.

It appears that the Borg scale is more responsive to change following an intervention, such as pulmonary rehabilitation, than the VAS as it has demonstrated a larger effect size (> 0.92 *versus* > 0.48) (46, 205, 209, 213). It is noteworthy that the modified Borg scale and VAS only use one question to evaluate a particular construct, such as the severity of dyspnoea. Because these scales are single-item tools, it is difficult to evaluate internal consistency; the extent to which individual items in a questionnaire scale measure the same construct, using conventional methods such as Cronbach’s coefficient alpha (214).

2.3.3.1.3 Oxygen Cost Diagram

The OCD is a type of VAS consisting of a 100 mm long vertical line with descriptive phrases of 13 daily activities located at various points along the line corresponding to oxygen requirements at different activity levels (215). People indicate the point above which they would become breathless, with higher scores indicating fewer impairments due to dyspnoea (215). However, not all people engage in all the activities listed on the OCD (216), and people have demonstrated difficulty in understanding how to use the diagram (217). The OCD relies mainly on ambulatory activities, which makes it difficult to use for evaluating those who are dyspnoeic at rest. The OCD has been shown to be reliable (intra-class correlation coefficient [ICC] = 0.64), two weeks apart, and scores demonstrated an association of moderate strength with the 6MWD (r = 0.49, $p < 0.5$) in those with pulmonary disease (218). The OCD has been shown to be responsive to bronchodilators, such as salbutamol, in those with chronic airflow limitation (22), with a medium effect size (0.5) (206).

2.3.3.1.4 Medical Research Council dyspnoea scale

The MRC dyspnoea scale is a simple categorical scale that is commonly used to assess functional limitation resulting from dyspnoea (19). It consists of a five-point

scale ranging from 1 ('Normal: only get breathless with strenuous exercise') to 5 ('Very severe: too breathless to leave the house or breathless on dressing'). The individual selects the most appropriate item. The MRC dyspnoea scale has been shown to be useful when categorising people with COPD based on their level of functional limitation due to dyspnoea (26) and has been associated with five years survival ($p < 0.001$) (26). The MRC dyspnoea scale is one of four variables, together with body-mass index, FEV_1 and the 6MWD, which comprise a multidimensional grading system, known as the BODE index (Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity), that can be used to predict survival in people with COPD (219). The MRC dyspnoea scale has been shown to have strong associations with the OCD (r = 0.70) and the baseline dyspnoea index (BDI) (r = 0.83, all $p < 0.001$) (220). The MRC has not demonstrated responsiveness (160). Because the MRC dyspnoea scale focuses on functional limitations due to dyspnoea, it does not provide a quantification of dyspnoea intensity or an assessment of associated distress and effort.

2.3.3.2 Multidimensional tools

2.3.3.2.1 Baseline Dyspnoea Index and Transitional Dyspnoea Index

The BDI and the Transitional Dyspnoea Index (TDI) were specifically designed for the evaluation of dyspnoea (20). Developed as a discriminative tool, the BDI evaluates three dimensions of dyspnoea: functional impairment, magnitude of effort and magnitude of task at a single point in time (20). This tool rates an individual's dyspnoea in each of these domains on a scale from 0 ('severe or extraordinary impairment') to 4 ('no impairment'). The TDI is a companion scale used to track changes from baseline over time and can be used to evaluate the effect of therapeutic interventions (221). The TDI measures changes in dyspnoea over time in the three BDI domains on a scale from -3 ('major deterioration') to +3 ('major improvement') (20). The BDI/TDI have been reported as being a reliable tool in people with pulmonary disease including COPD, with interrater agreement at baseline and transition focal scores of 92% and 90%, as well as weighted kappa value of 0.7 and 0.6 respectively (20). In addition, the BDI has been shown to have a moderate association with the 12-minute walk distance (r = 0.60) and a weak association with FEV_1 (r = 0.41, all $p < 0.01$) in 38 people with respiratory diseases, of whom 32 had

COPD (20). The TDI has been shown to have a weak association with the change in 12-minute walk distance (r = 0.33, *p* = 0.04) (20). Thus, the BDI/TDI have been considered as valid tools to assess dyspnoea in COPD. However, overall, the strength of the associations of the BDI/TDI with other measures was weak and that study is very old. Therefore, in order to increase the utilisation of the BDI/TDI in all settings it would be advantageous to re-assess the validity of the BDI/TDI in COPD populations with available dyspnoea tools that have been validated in people with COPD. The minimum clinically important difference for the TDI has been determined as one unit improvement from the BDI (222). This finding was reported in a retrospective study of 997 people with stable COPD who participated in a randomised controlled trial evaluating the effect of triotropium. It would be advantageous to repeat the analyses of clinically significance difference for the TDI in a prospective trial. The BDI and TDI were developed to be administered by an interviewer, and several studies have been performed using these versions (217, 222, 223). Mahler et al (193) developed self-administered BDI/TDI versions and showed that these versions demonstrated a strong association with the interviewer-administered versions (BDI: r = 0.83; TDI: r = 0.94; $p < 0.001$ for both). Using the self-administered BDI/TDI version, Mahler et al (224) found that, 36 of 65 people reported no change in functional limitation resulting from dyspnoea measured by the MRC scale following a standard therapy. These 36 people reported a clinically important change of > 1unit in the TDI, indicating that the BDI/TDI is more sensitive to change compared to the MRC scale. Although the BDI/TDI are activity determined that measure dyspnoea with specific activities, it does not provide an assessment of emotional response to dyspnoea.

2.3.3.2.2 University California, San Diego Shortness of Breath Questionnaire

The University of California, San Diego Shortness of Breath Questionnaire (SOBQ) is a self-reported scale originally designed as a clinical instrument to screen people for suitability to participate in pulmonary rehabilitation (225). The SOBQ comprises 24 items that evaluate dyspnoea associated with a variety of daily activities during the preceding week. People are required to rate their dyspnoea when undertaking 21 different activities on a scale ranging from 0 (‘not at all’) to 5 (‘maximal or unable to do because of dyspnoea’). In addition, people are required to rate three additional

questions related to fear of harm from over-exertion and fear of dyspnoea. In 143 people with COPD, the SOBQ has been shown to have acceptable reliability over two days (r = 0.94, $p < 0.01$) and excellent internal consistency (Cronbach's alpha = 0.91) (181). The validity of the SOBQ has been shown through a moderate association with the 6MWD (r = 0.47, $p < 0.05$) and a weak association with FEV_1% predicted (r = 0.28, $p < 0.05$) (181). However, it would be advantageous to re-assess the validity of the SOBQ with available tools that have already been validated in people with COPD, and to investigate whether this questionnaire is reliable and valid to be used in different cultures. The SOBQ has been shown to decrease by 20% following eight weeks of pulmonary rehabilitation, representing an improvement in dyspnoea (195). For any activities that people do not perform, they are asked to estimate their level of dyspnoea for that activity. it should also be kept in mind that some people may not have the reading skills required to complete the questionnaire accurately and may need help, uncontrolled factors that are not always easy to detect but that could affect validity. Although this questionnaire is long, it only attempts to address aspects of the emotional response to dyspnoea as indicated by perceived fear, and this is only in response to specific activities.

2.3.3.2.3 Pulmonary Functional Status and Dyspnoea Questionnaire

The Pulmonary Functional Status and Dyspnoea Questionnaire is a self-administered, 164-item questionnaire that evaluates dyspnoea and activity levels (226). Lareau et al (21) developed a shorter version: the Pulmonary Functional Status and Dyspnoea Questionnaire—Modified version (PFSDQ-M). The modified version contains 40 items measuring dyspnoea, fatigue and functional status. It has variable Likert-type scales and the mean score for each subscale and total score can be calculated, responses with a lower score indicative of greater impairment (21). The dyspnoea domain evaluates the ability of an individual to perform different activities and any associated dyspnoea. The PFSDQ-M has been demonstrated to be reliable (ICC = 0.83) and have reasonable internal consistency (Cronbach's alpha = 0.80) in 50 people with stable COPD (21). The validity of this tool has been demonstrated via moderate to strong associations with the Sickness Impact Profile and 12-minute walk distance (r = 0.52 and r = 0.62), respectively, all $p < 0.001$) (21). The PFSDQ-M has been shown to improve one year after short-stay pulmonary rehabilitation in 34

people with COPD ($p < 0.001$) (227). However, the PFSDQ-M is lengthy and does not evaluate dyspnoea aspects such as the quality of dyspnoea and the emotional response to dyspnoea.

2.3.3.2.4 Multidimensional dyspnoea profile

The Multidimensional Dyspnoea Profile (MDP) is a questionnaire that measures the immediate intensity, immediate unpleasantness, sensory quality and emotional response to dyspnoea components (228). This questionnaire is proposed to refer to a specific event or period of time. Therefore, the user needs specify a "focus period", such as "after you climb three flights of stairs", "the last minute of breathing on the mouthpiece" or "right now" (229). The MDP includes 12 items: an immediate sensory intensity item, an immediate unpleasantness item, five items related to sensory qualities (e.g. work/effort, chest tightness/constriction), and five items addressing emotional response (e.g. anger, frustration). All items are rated on a scale of 0 to 10, with higher scores representing greater intensity, unpleasantness or distress. However, the items of MDP appear to be allocated as sensory or emotional components without robust testing for their psychometric properties. The use of both psychophysical and psychometric approaches to validate the MDP is important in the field of dyspnoea measurement instruments in order to increase the confidence of using this tool (229).

The five items on the sensory quality component are descriptors similar to those found in the literature on the language of dyspnoea (29, 33, 230). The MDP descriptors were selected using inter-correlations between item responses from an earlier study involving 104 people with COPD (231). The emotional response items on the MDP include 'depression', 'anxiety', 'frustration', 'anger' and 'fear'. These items appear to be extrapolated from pain research due to the similarity between dyspnoea and pain in terms of emotional response component (232-234).

Meek et al (235) demonstrated that acceptable reliability (test-retest reliability, ICC > 0.90) and internal consistency (Cronbach's alpha > 0.80) of the of MDP in 151 people with cardiopulmonary diseases, including COPD (n = 41), over a time period of one hour. However, this time period, one hour, between test-retest is an insufficient time period as it could allow respondents to recall their initial responses.

Approximately two weeks is often considered generally appropriate time interval between test-retest (236).

The validity of the MDP was demonstrated by significant associations between both components of the MDP and the MRC grades (both r > 0.34). Similarly, associations were found between the scores for components of the MDP and the PFSDQ-M scores for dyspnoea and fatigue (r > 0.56) and the scores for anxiety and depression components of the Brief Symptom Inventory (r > 0.66 and r > 0.54, respectively, p = 0.01 for all) (235). Meek et al (235) also showed that the MDP was responsive to change following an AECOPD (a small effect size of 0.38). Given the small proportion of COPD participants and an insufficient time period between test-retest, further study testing psychometric properties of the MDP in people with COPD is required in order to increase the confidence of using this tool.

2.3.3.2.5 Dyspnoea-12 questionnaire

The Dyspnoea-12 (D-12) questionnaire measures the severity of dyspnoea (23). Compared with the MDP, the D-12 was derived from the large pool of dyspnoea descriptors assembled. More than 300 people with COPD, interstitial lung disease (ILD) and chronic heart failure participated in the study to develop the D-12 (237).

The D-12 provides an overall score for the direct effect of dyspnoea and incorporating quality and emotional response components. The quality component includes items such as ‘my breathing requires more work’ and ‘my breathing is exhausting’. The emotional response component relates to the emotional effect of dyspnoea and includes items such as ‘my breathing makes me feel depressed’ and ‘my breathing is distressing’ (23). The overall score is calculated by adding the responses for each item (0 = none to 3 = severe). The total D-12 score ranges from 0 to 36, with higher scores indicating greater severity (237). This tool is simple and quick to use for assessing dyspnoea in clinical practice (23, 237).

The D-12 does not rely on a reference level of activity, such as taking a bath or walking up stairs, or on any specific type of activity. The reference frame ‘these days’ reflects the current level of dyspnoea experienced by people in their daily life as opposed to dyspnoea experienced in response to a specific activity or on the day of the test (237). This time reference may be very useful in identifying and tracking

dyspnoea in daily life over weeks or months but is not suitable for evaluating dyspnoea at a specific time or with a specific activity or intervention.

In a study of 153 people with COPD, Yorke et al (23) reported that the D-12 has acceptable internal reliability (Cronbach's alpha = 0.9) and acceptable test-retest reliability (ICC = 0.90), with a median of 16 days for retest reliability. The validity of the D-12 has been demonstrated through weak to moderate associations with HADS (anxiety: r = 0.51 and depression: r = 44) and with FEV_1 (r = -0.30), 6MWD (r = -0.38) and MRC grades (r = 0.48) ($p < 0.05$ for all) in 53 people with COPD (23). In addition, the D-12 has been demonstrated to be reliable two weeks apart in 84 people with ILD (ICC = 0.94) (41), 102 people with asthma (ICC = 0.93 to 0.96) (40) and 176 people pulmonary arterial hypertension (ICC = 0.90) (42). The validity of the D-12 has been demonstrated through strong associations with total score of SGRQ domain (r > 0.78, $p < 0.001$), moderate association MRC grades (r > 0.59, $p < 0.001$) and weak to moderate association with HADS (anxiety: r = 0.35 to 0.57 and depression: r = 0.22 to 0.59, $p < 0.05$) in those with ILD and asthma (40, 41). Furthermore, in those with pulmonary arterial hypertension, the D-12 was shown to be strongly associated with the Minnesota Living with Heart Failure Questionnaire – Pulmonary hypertension modified version, measures the effects of heart failure symptoms, functional limitations and psychological distress on an individual's quality of life (r = 0.70, $p < 0.01$), and moderately and strongly associated with anxiety and depression, measured using the HADS (r = 0.54 and r = 0.68, $p < 0.001$, respectively) (42).

The D-12 has been successfully translated to the Korean language and is a reliable and valid tool for measuring dyspnoea in people with tuberculous destroyed lung and bronchiectasis (43). However, this instrument has not yet been tested for responsiveness to interventions, such as bronchodilators or pulmonary rehabilitation. In this thesis, given the simplicity of the D-12 in terms of assessing the intensity, quality and emotional response of dyspnoea and the lack of tools to measure dyspnoea in Saudi people with COPD, the D-12 was translated to the Arabic language and then tested for reliability, validity and responsiveness to change in a clinical condition over time.

2.3.3.3 Dyspnoea embedded in health-related quality of life questionnaires

A number of questionnaires have been designed to assess the overall impact of COPD on an individual's HRQoL. Disease-specific HRQoL questionnaires may include components that evaluate the effect of dyspnoea on quality of life. It is important to note that single components may not provide the same psychometric properties when used without the rest of the instrument. These scales often require the respondent to recall activities associated with dyspnoea.

2.3.3.3.1 Chronic Respiratory Disease Questionnaire

The Chronic Respiratory Disease Questionnaire (CRDQ) includes 20 items that evaluate an individual's outcomes, with a focus on four dimensions of disease: dyspnoea, fatigue, emotional function and the individual's feeling of control or mastery over the disease (22). This questionnaire has been widely used to quantify the effect of COPD on an individual's HRQoL (200, 238). The CRDQ is available in four different versions for clinical use: the original interviewer-administered CRDQ with an individualised dyspnoea domain, an interviewer-administered CRDQ with a standardised dyspnoea domain, a self-administered CRDQ with an individualised dyspnoea domain and a self-administered CRDQ with a standardised dyspnoea domain. The individualised dyspnoea domain in the CRDQ requires the individual to identify five activities from a list of 25 common activities that they have undertaken during the past two weeks, which are important to them and during which they have experienced breathless (22). The dyspnoea severity is evaluated on a seven-point scale, ranging from 1 ('most dyspnoea') to 7 ('least dyspnoea') (22). An interviewer-administered CRDQ with both individualised and standardised dyspnoea domains appears to be appropriate for those illiterate people with COPD.

While an interviewer-administrated CRDQ with both individualised and standardised dyspnoea domains may help to avoid missing responses and errors in completing the CRDQ, an interviewer led questionnaire can be very time consuming (239, 240). This led to the development of a self-administered CRDQ with a standardised dyspnoea domain (241). The standardised dyspnoea domain in the CRDQ includes standardised activities that ask the people to indicate how much shortness of breath they have experienced while performing each of the activities (242). The dyspnoea

severity is evaluated similarly to the individualised version (242). The dyspnoea domain of the CRDQ can be considered on its own (221).

In people with COPD, the individualised version of CRDQ has been demonstrated to have acceptable test-retest reliability (ICC = 0.73), but the dyspnoea domain has shown low internal consistency (Cronbach's alpha = 0.53) (243). This low internal consistency could indicate it may not have identical psychometric properties when used in isolation from the scale in its entirety. However, the dyspnoea domain of the CRDQ has been found to strongly associate with the VAS ($r = 0.66$, $p < 0.05$) (244). Another study (53) also showed moderate to strong associations between scores from the dyspnoea domain of the CRDQ with TDI scores and FEV_1 ($r = 0.78$, $r = 0.48$, respectively; $p = 0.0001$ for all). The dyspnoea domain score of the CRDQ increased significantly by a mean of 1.6 point per item (ppi) during the recovery periods following an AECOPD (24) and 0.79 ppi following pulmonary rehabilitation compared to those who received usual care (45). A mean change of 0.5 ppi within a domain is considered clinically important (245).

2.3.3.3.2 St. George's Respiratory Questionnaire

The SGRQ is a self-administered, 76-item questionnaire measuring disease HRQoL (246). This questionnaire measures three domains: symptoms, activities and impact on daily life. Dyspnoea is evaluated in terms of its effect on daily activities, using a specific 'activity' domain. It is also evaluated using the 'symptoms' domain in conjunction with information pertaining to coughing, sputum production and wheezing. However, dyspnoea is not assessed as a separate domain in the SGRQ. Therefore, it is difficult to identify the impact of dyspnoea on HRQoL.

Jones et al (246, 247) reported on the reliability, validity and responsiveness of the SGRQ. The reliability of the SGRQ has been demonstrated over a two-week retest reliability period involving 40 people with stable asthma (ICC = 0.91) and 20 people with stable COPD (ICC = 0.92) (246). The reliability for the sub-components was considered acceptable (ICC = 0.91 for symptoms; ICC = 0.87 for activity; ICC = 0.88 for impact on daily life) (246). The SGRQ has been demonstrated to be valid through a moderate to strong association with the MRC grades ($r \geq 0.46$, $p < 0.05$) (247, 248) and with anxiety ($r \geq 0.57$, $p < 0.05$) and depression ($r \geq 0.57$, $p < 0.05$),

measured using HADS (246). A Cochrane review concluded that the SGRQ changed significantly by 6.89 units for the total scores following a pulmonary rehabilitation compared to those who received usual care (45). A mean change of 4.0 units is considered clinically important (45, 249).

In summary, dyspnoea can be measured using unidimensional, multidimensional, and HRQoL tools that include assessment of dyspnoea. Most of the available dyspnoea tools focus on assessing behaviours such as activity limitation. Few tools attempt to quantify individual's perception of the experience of dyspnoea and its direct impact on how the individual feels. Most notable, is the absence of evaluating the emotional response to dyspnoea in all tools except the MDP and D-12.

2.3.4 Interventions to reduce dyspnoea in COPD

2.3.4.1 Changing the inhaled gas

2.3.4.1.1 Oxygen

Supplemental oxygen is part of the standard care for the treatment of people with COPD who experience chronic hypoxemia, defined as partial pressure of oxygen in arterial blood < 55 mmHg, and its ability to relieve dyspnoea has been demonstrated (13, 250-252). The beneficial effect of oxygen could be associated with stimulation of receptors related to gas flow via the upper airway (253) and/or changes in chemoreceptor stimulation, leading to changes in the pattern of breathing (254, 255).

2.3.4.1.2 Heliox

Heliox is a helium-oxygen mixture that is known to be nontoxic, noncarcinogenic and have no lasting impacts on any human organ systems (256). The short-term use of heliox has been shown to result in reductions in dyspnoea outcome measures in people with stable COPD and during exacerbations (257-261). Heliox decreases the resistance to airflow, which may reduce the work of breathing, decrease the rate of hyperinflation, improve exercise capacity and decrease dyspnoea in people with COPD (257, 258, 262). However, there is no evidence related to the long-term use of heliox in people with COPD. Compared with oxygen, heliox is more expensive (263).

2.3.4.2 Pharmacological approaches

2.3.4.2.1 Opioids medications

Short-term administration of opioids can be used for the treatment of dyspnoea in people with COPD and has been demonstrated to reduce dyspnoea (264-266). Opioids may have multiple mechanisms of action leading to decreased dyspnoea, including reductions in ventilation, oxygen consumption, sensitivity to hypercapnia, the central perception of dyspnoea and anxiety related to dyspnoea (267). Opioids can be administered either in oral, parental or nebulised forms (13). Oral morphine is the most common prescribed opioid for decreasing dyspnoea (264). Other opioids medications include dihydrocodeine, diamorphine, fentanyl, hydromorphone, and oxycodone (264). Opioids are associated with side effects, particularly constipation, but the development of respiratory depression is not common with the doses used to treat dyspnoea (13).

Other pharmacological agents including bronchodilators, anxiolytic medications, antidepressants, phenothiazines, inhaled furosemide and inhaled lidocaine are used to reduce dyspnoea. However, these medications have been found to be either ineffective or there are insufficient data to recommend their use in people with COPD (13, 264).

2.3.4.3 Non-pharmacological approaches

2.3.4.3.1 Pulmonary rehabilitation

Pulmonary rehabilitation is defined as an evidence-based, multidisciplinary and comprehensive program of care for people with COPD, with exercise training considered the key component of pulmonary rehabilitation (268). The beneficial effects of pulmonary rehabilitation include reductions in exertional dyspnoea and leg fatigue, improved exercise capacity and HRQoL, decrease in the risk of hospitalisation for exacerbations and reduced mortality (45, 269, 270). Exercise training leads to improvements in skeletal muscle function of people with COPD (271, 272). Further, the increased oxidative capacity of the skeletal muscles leads to a decreased ventilatory demand for a given submaximal work rate; this reduces dynamic hyperinflation and decreases exertional dyspnoea (273, 274). A recent

Cochrane review included 19 randomised controlled trials that measured dyspnoea intensity after pulmonary rehabilitation, using the dyspnoea domain of the CRDQ, in people with COPD (45). The review concluded that people allocated to pulmonary rehabilitation who received at least four weeks of exercise training had, on average, a greater improvement in dyspnoea intensity compared with those allocated to control groups (mean difference = 0.79 ppi, 95% CI 0.56 to 1.03) (45). The mean difference exceeded the minimal clinically important difference (MCID) (0.5 ppi) (275).

2.3.4.4 Other non-pharmacological approaches

A number of strategies have been explored for their potential impact on reducing dyspnoea in people with COPD. Pursed-lip breathing is often a strategy used spontaneously by people with COPD to reduce dyspnoea (264). In addition, cool air provided by a fan is often reported by people with respiratory disease as means of reducing their dyspnoea (13). However, no studies have examined the use of fans and/or cool airflow for the reduction of dyspnoea intensity in people with COPD.

Non-invasive ventilation leads to decreased work of breathing which might reduce dyspnoea. Studies that assessed long-term nocturnal use of non-invasive ventilation in people with severe COPD demonstrated a significant reduction in dyspnoea perception (276, 277). In people with COPD, the use of non-invasive ventilation during exercise improves exercise tolerance (278, 279), which may facilitate the achievement of high work rates and optimise training response.

In summary, inhaled gases such as oxygen and heliox have been demonstrated to reduce the level of dyspnoea reported by people with COPD. Pharmacological and non-pharmacological approaches have also been shown to decrease the perception of dyspnoea in people with COPD.

Part 3

This part provides a definition for an AECOPD and information related to the causes of an AECOPD. The effects of an AECOPD on clinical outcomes and the economic burden of an AECOPD are also discussed. In addition, an overview of the management of an AECOPD is provided.

2.4 Definition and classification of severity of an AECOPD

An AECOPD is an acute event characterised by a worsening of the individual's respiratory symptoms that is beyond normal day-to-day variation and leads to a change in medication (10). The severity of an AECOPD is often classified as mild when the exacerbation of respiratory symptoms requires only a change of inhaled medication by the individual, without additional healthcare provider contact (10). An AECOPD is classified as moderate when the exacerbation of an individual's respiratory symptoms necessitates medical assistance, including a short course of antibiotics and/or oral corticosteroids, without requiring hospitalisation (10). An AECOPD is classified as severe when the exacerbation of the individual's respiratory symptoms requires hospitalisation (10).

2.4.1 Causes of an AECOPD

An AECOPD can be caused by infections and/or exposure to air pollutants. However one-third of causes of severe AECOPDs are unknown (280, 281).

2.4.1.1 Viral infections

An AECOPD can be triggered by upper respiratory tract infections, which are common during the winter months when respiratory viral infections are common in the community (282).Viruses have been detected in around half of those with exacerbations, depending on the diagnostic techniques used (283, 284). The most commonly isolated viruses are *human rhinoviruses*, *coronavirus, respiratory syncytial virus*, *influenza, parainfluenza,* and *adenovirus* (282-284). *Human rhinoviruses* can infect the lower airways and contribute to inflammatory changes during an AECOPD (282). In people with COPD, low-dose- experimental rhinovirus infection has been found to induce symptoms that are typical of an AECOPD, providing support that respiratory viruses can infect the lower airways (285). AECOPD that is caused by a viral infection is often more severe, associated with a prolonged recovery time and increases the risk of hospitalisation than an exacerbation caused by other factors (286, 287).

2.4.1.2 Bacterial infections

The precise role of bacteria in an AECOPD has been difficult to clarify as the bacteria found in the airways of people with COPD during periods of clinical stability are often associated with those isolated during an exacerbation (288-290). An AECOPD may result from a change in the colonising strain of bacteria (291), although not all exacerbations are associated with a change in bacterial strain, and not all bacterial strain changes cause anexacerbation. The common bacterial organisms are *Streptococcus pneumoniae, Haemophilus influenza* and *Moraxella catarrhalis*, and in people with more severe COPD, *Pseudomonas aeruginosa* (282, 292). The presence of lower airway bacterial colonisation in an individual during periods of clinical stability has been shown to be related to an exacerbation frequency (293). People with COPD who have their airways colonised by *Haemophilus influenza* during periods of clinical stability report more symptoms and increased sputum purulence during an AECOPD than those not previously colonised (293, 294). This suggests that lower airways bacterial colonisation in people with stable COPD modulates the character and frequency of an AECOPD (293, 294).

Up to 25% of AECOPDs are caused by bacterial and viral coinfection which is associated with more severe disease (295). An increase in the systemic inflammatory response has been found in exacerbations associated with both *Haemophilus influenzae* and *rhinovirus* isolation (288) These findings have been confirmed in a further study that revealed greater impairment in lung function and longer hospitalisations in people with an AECOPD associated with bacterial and virus coinfection compared with those without coinfection (295).

2.4.1.3 Air pollutants

The role of air pollution in causing an AECOPD has been investigated in epidemiological studies that have demonstrated that increases in sulphur dioxide, nitrogen dioxide, particulate matter under 10 microns in diameter and black smoke particles are associated with worsening chronic respiratory symptoms and an increased mortality rate in people with COPD (296-298). These studies investigated the rate of hospital admission for an AECOPD at times of increased levels of atmospheric pollution and concluded that effects of air pollution on hospital

admission are significant, and could account for approximately 6 to 9% of all admissions for an AECOPD, depending on the time of year (299).

2.4.2 Effects of an AECOPD on clinical outcomes

An AECOPD can have serious clinical consequences such as worsening respiratory symptoms and reduced lung function, specifically a decline in the FEV_1 (91). In addition, a decrease in HRQoL (92), functional capacity and physical activity, increased feelings of anxiety and depression, and higher risk of mortality have been demonstrated during an AECOPD (91, 92).

2.4.2.1 Symptoms

An AECOPD is associated with worsening dyspnoea and changes in sputum purulence and/or volume (25, 300). One of the first studies that tracked changes in respiratory symptoms, using daily diary cards, reported on 504 exacerbations experienced by 91 people with moderate to severe COPD over two and half years (25). The study found that, on the day of onset of an exacerbation, symptoms increased sharply with 64% of exacerbations associated with dyspnoea and 26% with increased sputum volume and 42% with increased sputum purulence. Increases in minor symptoms such as cough and wheeze ranged from 12% to 35% (25). In people with COPD, dyspnoea is often the primary reason for seeking medical assistance during an AECOPD (13). Several studies have shown that people have reported a higher intensity of dyspnoea during an AECOPD compared to their dyspnoea intensity following an AECOPD (24, 53, 301). Parker et al (24), for instance, assessed 20 people during an AECOPD and 60 ± 5 days following an AECOPD using the dyspnoea domain of the CRDQ. The authors reported that, during an AECOPD people were more dyspnoeic during their usual activities of daily living than 41 days following the AECOPD (dyspnoea domain score of the CRDQ 2.4 *versus* 4.5 ppi) (24).

The trajectory of recovery for an AECOPD is variable. Parker et al (24), demonstrated that, following an AECOPD, 40% of 20 people with a moderate to very severe AECOPD reported that their levels of dyspnoea had not returned to pre-AECOPD levels within an average of 41 days. This suggests that the recovery period may be prolonged in a large proportion of people with COPD. Seemungal et al (25)

reported, in 101 people with a moderate to severe AECOPD, that 91% had returned to their pre- AECOPD levels of respiratory symptoms by 91 days following an AECOPD. The current evidence suggests that a follow-up period of ≥ 91 days is required to allow 91% of people with an AECOPD to recover following an AECOPD.

Fatigue is considered to be a major symptom experienced by people with COPD and has also been shown to increase during an AECOPD (117, 302). Baghai-Ravary et al (303) used the Functional Assessment of Chronic Illness Therapy-Fatigue Scale in 107 people with COPD during a period of clinical stability and during an AECOPD. The authors found that those who had an AECOPD (n = 32) experienced a 24% increase in fatigue ($p < 0.001$) during an AECOPD (severity of an AECOPD was not reported) compared with a period of clinical stability (303). Furthermore, people who had frequent AECOPDs (≥ 2 exacerbations per year) experienced more fatigue than those who had infrequent AECOPDs ($p = 0.002$) (303). The study also demonstrated that only those people (53%) who had infrequent AECOPDs reported that their fatigue levels had returned to pre-AECOPD levels within six weeks after an AECOPD (303).

2.4.2.2 Exercise capacity

In people with COPD who have decreased functional exercise capacity, a further decrease in exercise capacity during an AECOPD has been reported (302, 304, 305). For instance, Carr et al (302) measured functional exercise capacity, using the 6MWD, in 34 people with stable moderate to severe COPD at the completion of pulmonary rehabilitation, and followed up them for six months until they had an AECOPD. The authors found a reduction of 16% in the 6MWD two weeks following a moderate to severe AECOPD (302). This magnitude of reduction is similar to that observed between the first week of an AECOPD and at one month following hospital discharge (19%) (304). Furthermore, the reduction of exercise capacity following an AECOPD persisted over the two years of follow-up (306). In addition, people with frequent AECOPDs (≥ 2 exacerbations per year) had lower functional exercise capacity than those who had infrequent AECOPDs (p = 0.006), with a mean difference of 51 meters in the 6MWD (306), seen which is greater than the MCID (30 meters) (307).

2.4.2.3 Physical activity

The level of physical activity of people with COPD reduces in response to an AECOPD (304, 308, 309). Consistent findings were reported by Pitta et al (304) and Borge et al (310) who used accelerometers (DynaPort McRoberts; The Hague, Netherlands) to measure the physical activity of people hospitalised for AECOPD. They demonstrated that a large proportion (> 86%) of people' waking hours were spent sitting and lying down during hospitalisation. One month after discharge, Pitta et al (304) demonstrated that the time spent in sitting and lying down did not significantly differ than that seen during hospitalisation. Borge et al (310) reported that, one month after discharge, the proportion of time spent sitting and lying down reduced to approximately 67% of waking hours ($p < 0.001$). The differences in the findings between the two studies could be explained in part by the people included in the studies. Borge et al (310) included those who had less severe COPD and higher functional exercise capacity at one month after discharge compared to those included in the study by Pitta et al (304) (FEV_1% predicted, 49% *versus* 34% and 6MWD, 373 m *versus* 332 m, respectively). Decreases in FEV_1 and 6MWD have been associated with low levels of physical activity in people with COPD (56, 85), which could influence the recovery of physical activity following hospital discharge.

A reduction in physical activity has also been demonstrated in those who had an AECOPD without hospitalisation (i.e. a mild or moderate AECOPD). Using a pedometer (a Yamax Digiwalker SW-200), Alahmari et al (309) reported a reduction of 12% in the daily step counts of 73 people with moderate to severe COPD between a period of clinical stability and the first seven days of a mild to moderate AECOPD ($p = 0.045$). The same study also revealed that those with frequent exacerbations (≥ 2 exacerbations per year) had a greater decrease in daily step counts over time than those with infrequent exacerbations (707 *versus* 337 steps per year, $p = 0.002$) (309). These data imply that people with frequent AECOPD (≥ 2 exacerbation per year) participated in a little physical activity than those with infrequent AECOPD (309).

2.4.2.4 Health-related quality of life

Studies that used disease–specific HRQoL questionnaires, such as the SGRQ and the CRDQ, during and following an AECOPD, showed a reduction in HRQoL during an

AECOPD (92, 302, 306, 311, 312). Although impairments in HRQoL have been reported during an AECOPD, it appears that people with frequent exacerbations have more impairment in their HRQoL than those with infrequent exacerbations (92, 311, 313). Furthermore, regardless of the criteria used to define frequent AECOPDs, people with frequent AECOPDs tend to have greater HRQoL deterioration over time compared with those who had infrequent AECOPDs. Spencer et al (314), for instance, demonstrated that people with frequent exacerbations (≥ 1.65 exacerbations per year) had more rapid deterioration in HRQoL (mean of 2.9 units per year), assessed by the SGRQ, compared to those with infrequent exacerbations (mean of 2.4 units each year) ($p < 0.001$) (314).

The time course for recovery of HRQoL varies following an AECOPD (314). During the first month following an AECOPD, greater improvements were reported amongst those who had only one AECOPD compared with those who had more than one AECOPD ($p < 0.05$) over six months of follow-up (301, 314). After the first month, HRQoL improved for people with only one AECOPD and this improvement was persisted up six months (314). In contrast, the HRQoL of those who experienced two or more AECOPDs, remained unchanged after the first month of improvement (301, 314). These results indicate that HRQoL may take several months to return to pre-AECOPD levels in those who experience multiple AECOPDs.

2.4.2.5 Feelings of anxiety and depression

Feelings of anxiety and depression are common among people with COPD and also appear to be associated with an AECOPD (315, 316). However, there are limited data on whether the feelings of anxiety or depression are altered during an AECOPD. Thompson et al (317) measured anxiety and depression using the HADS amongst 40 people with a severe AECOPD on admission to the hospital. Thirty-two (80%) people reported feelings of anxiety (HADS scores ≥ 8) on admission. These HADS scores remained unchanged over a median of 14 weeks of follow-up after discharge. Although an improvement in the score of depression was observed over the same follow-up period (depression HADS scores mean difference = 2.5), this improvement was not statistically different to that reported on admission ($p > 0.05$) (317). The lack of statistical significance may be explained in part by the small sample size. In addition, feelings of anxiety and depression may require a longer time frame to

return to pre-AECOPD levels. Quint et al (318) used the Center for Epidemiologic Studies Depression Scale in 169 people with moderate COPD to assess depression. Over a one year follow-up, the authors demonstrated that feelings of depression during an AECOPD increased compared to that reported during a period of clinical stability (20.3 ± 10.4 *versus* 14.6 ± 11.8, $p < 0.001$) (318). In addition, people with frequent exacerbations (≥ 3 exacerbations per year) had more feelings of depression than those without frequent exacerbations ($p = 0.03$) (318).

2.4.2.6 Lung function

Several studies have investigated the effect of an AECOPD, regardless of severity, on lung function (91, 312, 319, 320). Specifically, these studies showed a relationship between accelerated decline in the FEV_1 and an AECOPD. Compared to the FEV_1 value obtained during a period of clinical stability, FEV_1 has been shown to be reduced by approximately 20% in people during a moderate to severe AECOPD (24). A similar decrease in the FEV_1 (16%) during a moderate to severe AECOPD was reported by Cote et al (306). The authors reported that this decrease persisted and did not return to pre-AECOPD levels over two years of follow-up.

The FEV_1 of people with more frequent AECOPDs has been shown to deteriorate more quickly than that of people who had infrequent AECOPDs (91, 320, 321). Donaldson et al (91) demonstrated that the decline in the FEV_1 over four years was 25% higher in people with moderate to severe COPD who experienced frequent exacerbations (> 2.92 exacerbations per year) than those with less frequent exacerbations.

2.4.2.7 Mortality

Several studies have revealed a high mortality rate in people with COPD who were hospitalised for an AECOPD (322-324). In people with a severe AECOPD, the mortality rate during hospitalisation was 8% (325) and increased to 23% after one year of follow-up (325, 326). Sprooten et al (326) demonstrated that those who were re-hospitalised early (within 49 days) had a mortality rate of 40%. The mortality rate for people with a severe AECOPD increases over time (327). Over a 17-year follow-up, the rate of mortality for people who had experienced a severe AECOPD was 50% at 3.6 years, 75% at 7.7 years and 96% by 17 years (327). In addition, the risk of

mortality has been show to increase with increasing frequency of AECOPD, regardless of other prognostic factors such as age, body mass index, FEV_1 and comorbidities (324). Thus, people with frequent AECOPDs (≥ 3 exacerbations per year) had the highest rate of mortality, with a 4.1 times higher risk of death (95% CI, 1.80 to 9.45) (324) than people with infrequent AECOPDs or those with 1 to 2 AECOPDs per year.

In summary, an AECOPD is associated with worsening symptoms and greater impairments in exercise capacity, physical activity, HRQoL and lung function. Increased feelings of anxiety and depression as well as increased rate of mortality are also associated with an AECOPD.

In people with a severe AECOPD, the mortality rate during hospitalisation was 8% (325) and increased to 23% after one year of follow-up (325, 326). The latter study (326) demonstrated that those who were re-hospitalised early (within 49 days) had a mortality rate of 40%. The mortality rate for people with a severe AECOPD increases over time (327). Over a 17-year follow-up, the rate of mortality for people was 50% at 3.6 years, 75% at 7.7 years and 96% by 17 years (327). In addition, the risk of mortality increased with increasing frequency of AECOPD, regardless of other prognostic factors such as age, body mass index, FEV_1 and comorbidities (324). Thus, people with frequent AECOPDs (≥ 3 exacerbations per year) had the highest rate of mortality, with 4.1 times higher risk of death (95% CI, 1.80 to 9.45) (324) than people with infrequent AECOPD or those with 1 to 2 AECOPDs per year.

In summary, an AECOPD is associated with worsening symptoms and greater impairments in lung function, HRQoL, exercise capacity and physical activity. Increased feelings of anxiety and depression as well as increased rate of mortality.

2.4.3 Economic burden of an AECOPD

A significant portion of COPD treatment costs are associated with an AECOPD (112). Furthermore, the severity and frequency of an AECOPD influences health care costs (112, 328). A retrospective study carried out in the United States of America and published in 2012 (329) included 8,554 people with COPD (329). The study showed that the annual total expense for health care (i.e. hospital admissions, emergency room, physician office visit and medications) was $4,720 USD for people

who had one or more AECOPDs compared with $1,425 USD for people who had no AECOPD. The annual cost for people with a severe AECOPD was approximately four times higher than those with a moderate AECOPD ($12,765 USD *versus* $3,356 USD). Equivalent data for costs associated with an AECOPD in Saudi Arabia are not available.

The burden of an AECOPD is not only reflected in direct costs, but also in indirect costs (113). Indirect costs including lost wages of the individual, lost wages of family caregivers, and employer-borne costs such as absenteeism and sick leave, disability and impaired work performance. The indirect costs of lost work days associated with an AECOPD have been estimated to account for 14% of the total AECOPD treatment cost (330).

2.4.4 Management of an AECOPD

The goals of management for an AECOPD are to reduce the impact of the current exacerbation and prevent subsequent exacerbations from developing (10). Depending on the severity of an AECOPD, people can be managed at home or at hospital (10). Home management of an AECOPD is common for people with less severe exacerbations and includes increasing the dose or frequency of existing bronchodilator therapy (10, 331). Hospital management of an AECOPD involves oxygen therapy, pharmacological therapy and may include ventilatory support.

2.4.4.1 Hospital management

2.4.4.1.1 Pharmacological therapy

There are three classes of medications commonly used for an AECOPD, namely bronchodilators, corticosteroids and antibiotics (10, 331).

Bronchodilators: Despite there being no controlled trials, short-acting inhaled β_2-agonists (e.g. salbutamol and terbutaline) with or without short-acting anticholinergics (ipratropium) are often the preferred bronchodilators for treatment of an AECOPD in order to minimise respiratory symptoms and to maximise bronchodilation (331-333). Inhaled bronchodilators can be delivered by nebulisers and metered dose inhalers with spacer device. Nebulisers and meter dose inhaler have been found to have equal efficacy in relieving an AECOPD, with no significant

difference in duration of hospitalisation (334). The dose of 5mg of salbutamol delivered by nebuliser is equivalent to 8 to 10 puffs of 100 mcg salbutamol delivered by metered dose inhaler and spacer (331). High doses of β2-agonists may lead to a decrease in the level of serum potassium (hypokalaemia) and predispose to irregular heartbeats (cardiac arrhythmias) (331). In the case of a severe AECOPD and insufficient response to short-acting bronchodilators, oral or intravenous methylxanthines (theophylline or aminophylline) can be considered (10).

Glucocorticosteroids: Oral, inhaled or intravenous glucocorticosteroids are beneficial in treating people with an AECOPD (10, 331, 335). In addition to bronchodilator therapy (plus oxygen therapy), glucocorticosteriods are recommended for the management of an AECOPD (10, 336, 337) as they decrease recovery time and improve FEV1 (336, 337). A dose of 30 to 50 mg of oral prednisolone per day for 10 to 14 days is a reasonable compromise between efficacy and safety (331). However, the optimal dose of glucocorticosteriods has not been established. A prolonged course and high dose of glucocorticosteriods can provide a long anti-inflammatory effect. However, glucocorticosteriods are associated with adverse effects, such as hyperglycemia, bone fractures, and osteoporosis, especially with the increasing doses due to the re-exacerbation of an AECOPD (331). A meta-analysis reported that use of glucocorticosteriods in COPD was associated with a modest but statistically significant increase in fracture risk. Each 500μg increase in glucocorticosteriod dose was associated with a 9% increase in fracture risk (338). Therapeutic guidelines (331, 339) reported that prolonged use of glucocorticosteriods (> 7.5 mg daily for more than 6 months) increases the risk of developing osteoporosis (331). it appears that lower doses of glucocorticosteriods are associated with fewer side effects and more benefit than higher doses in hospitalised people with an AECOPD (340).

Antibiotics: Given that bacteria are associated with a substantial proportion of episodes of AECOPD, the use of antibiotics is more effective when increased sputum purulence and volume is present (331). Oral antibiotics are preferred, for ease of administration, despite intravenous antibiotics can be given if there is difficulty in swallowing. A meta-analysis of 11 studies found that using antibiotics decreases the risk of short-term mortality by 78% and sputum purulence by 44% in people with an AECOPD (341). Therapeutic guidelines (331, 339) recommend the use of oral agents

of antibiotics such as doxycycline or amoxicillin is recommended. In case of people with an AECOPD do not respond or resistant organisms are suspected, amoxycillin–clavulanate must be prescribed (331). Although the use of antibiotics are recommended for seven to 10 days, optimal duration of antibiotics use has not been established (331, 339, 342).

2.4.4.2 Controlled oxygen therapy

During an AECOPD, oxygen administration is one of the primary therapies for people with hypoxaemia (10, 331). Controlled oxygen needs to be titrated to provide adequate levels of oxygenation (percutaneous oxygen saturation > 90%) (10).When oxygen is administered, arterial blood gases should be regularly checked in order to ensure there is adequate oxygenation without carbon dioxide retention or acidosis (10).

2.4.4.3 Ventilatory support

In people with a severe AECOPD who require ventilatory support, the primary objectives of mechanical ventilatory support are to reduce mortality and morbidity and to relieve symptoms (10). Mechanical ventilatory support during an AECOPD can be delivered non-invasively using positive pressure devices (by nasal or facial mask) or invasively (by endo/naso-tracheal tube or tracheostomy).

Findings of randomised controlled trials using non-invasive ventilation in acute respiratory failure have consistently produced success rates of 80% to 85% (343-345). Non-invasive ventilation has been shown to reduce respiratory acidosis (increases pH and decreases partial pressure of carbon dioxide in arterial blood) and reduce the severity of dyspnoea in the first four hours of treatment, and shorten the length of hospitalisation (331, 343, 346).

There are several indications for using invasive ventilation during an AECOPD of which one is the failure of an initial trial of noninvasive ventilation (10). However, there are major risks associated with invasive ventilation including the risk of ventilator-acquired pneumonia (especially when multiresistant organisms are prevalent), barotrauma, and failure to wean to spontaneous ventilation (10).

In summary, depending on the severity of an AECOPD, people can be managed at home or in hospital. Hospital management includes controlled oxygen therapy, pharmacological therapy and ventilatory support.

Part 4

This part reviews the literature pertaining to physical activity and sedentary behaviour, and public health recommendations on physical activity and sedentary behaviour for health. Various methods that are used to measured physical activity and sedentary behaviour, and factors associated with the measurement of physical activity and sedentary behaviour in people with COPD are also discussed.

2.5 Physical activity and sedentary behaviour

Physical activity can be defined as any bodily movement produced by skeletal muscles that results in energy expenditure above resting (basal) levels (54). When physical activities are planned, structured, repetitive and purposive in the sense that optimisation or maintenance of one or more components of physical fitness is the objective, it is known as exercise (347). Physical activity includes sport, exercise and physical activities performed as a part of people's daily living, occupation, transportation or leisure activities. Physical activity is often categorised as light, moderate or vigorous intensity, based on the level of energy expenditure required (348). For instance, light intensity physical activity includes energy expenditure ≥ 1.5 and < 3 metabolic equivalent units (METs). One MET represents the energy expenditure used during quiet rest and is frequently defined in terms of an oxygen uptake of 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$ (348). Light intensity physical activity involves activities such as ironing, slow walking, washing dishes and cooking food (348). Moderate intensity physical activity includes energy expenditure ≥ 3 and < 6 METs, and involves activities like dancing, brisk walking and sweeping the floor (348). Vigorous intensity physical activity requires an energy expenditure ≥ 6 METs and includes activities such as running, swimming, playing soccer, walking uphill and playing volleyball (348, 349).

Sedentary behaviour is characterised by low energy expenditure (< 1.5 METs) while in a sitting or reclining posture during waking hours (68, 350). It can occur throughout the waking day in different domains (i.e. across work, leisure, commuting and entertainment) (351). The most common sedentary behaviours are reading, sitting time, using the computer and television viewing (352).

2.5.1 Public recommendations on physical activity for health

The American College of Sports and Medicine (ACSM) guidelines recommend that adults undertake at least a minimum of 150 minutes of moderate intensity physical activity or 75 minutes of vigorous intensity physical activity each week, to maintain health benefits such as a reduction in cardiovascular and metabolic disease, and all-cause mortality (54). These beneficial effects have been proposed to be mediated by several physiological adaptations (54). These adaptations include improvement in endothelial function, production, expression and release of myokines by skeletal muscle, cardiovascular fitness and insulin sensitivity, maintenance of a healthy body weight, preservation of fat free mass, reduction in systemic inflammation and adiposity and/or improvements in immune function (54, 353). It appears that people who participate in regular prolonged periods of moderate to vigorous physical activity are more likely to have many of these physiological adaptations. This is supported by the current ACSM guidelines that recommend that adults perform at least 30 of daily moderate intensity physical activity, accumulated in bouts of at least 10 minutes in duration (54). It can be also achieved by performing a total of 75 minutes per week of vigorous intensity aerobic physical activity (54).

Daily step counting is a simple measure that is easily and directly translatable from the research to the clinical setting. In addition, it appears that it is meaningful for people trying to maintain or increase their physical activity, compared with other measures of physical activity such as METs. Therefore, there has been a growing interest in translating the current recommendation by the ACSM for moderate intensity physical activity into steps per day (62, 354, 355). Data pertaining to an appropriate translation of 30 minutes of moderate intensity physical activity in terms of daily steps were reviewed by Tudor-Locke et al (355), who concluded that 30 minutes of daily moderate intensity physical activity taken in addition to habitual daily activities in healthy older people is equivalent to accumulating at least 7,000 steps per day. These findings are consistent with the recommendation by the ACSM for adults to accrue at least 7,000 steps daily to confer health benefits (54). The review by Tudor-Locke et al (355) concluded that to meet the current recommendation for moderate intensity physical activity, steps can be also accumulated in a minimum of 3,000 steps in 30 minutes per day, which can be split

into 3 daily bouts of 1,000 steps for at least 10 continuous minutes for healthy older people (355).

2.5.2 Importance of reducing sedentary behaviour

Among those who participate in the recommended amount of physical activity, the proportion of total waking hours spent participating in physical activity is low, with a high proportion of time spent in either sedentary behaviour or light intensity physical activity (70). In the general adult population, a higher proportion of time in sedentary behaviour has been associated with a greater risk for all-cause of mortality (69, 356). This association is independent of the amount of time spent in moderate-to-vigorous intensity physical activity (69). The mechanisms for the association found include the minimal muscular contractions in the large postural muscles occurring during sitting (357), with the lower energy expenditure when compared with sedentary behaviours (358).

The manner in which sedentary time is accumulated appears to be important. Specifically, it has been shown that, regardless of the total time spent in sedentary behaviour, people who accumulated sedentary behaviour in prolonged unbroken bouts are at greater risk of developing cardiovascular and metabolic diseases compared to those who interrupted their sedentary time with either light or moderate intensity physical activity (71, 359). Despite a lack of sufficient evidence to provide firm recommendations about how often should we get up, a practical message may be to sit less throughout the day, and stand up at least every 30 minutes.

2.5.3 Quantifying physical activity and sedentary behaviour

Physical activity and sedentary behaviour can be measured using subjective methods (e.g. self-reported questionnaires) or objective methods (physical activity monitors such as pedometers and accelerometers).

2.5.3.1 Subjective methods

Subjective methods of measuring physical activity and sedentary behaviour include the use of questionnaires, diaries or logs, and surveys or interviews (360). These subjective methods are often inexpensive and easy to apply. However, the information they provide appears to be inaccurate (361), since people with COPD are

likely to overestimate the time spent walking and underestimate the time spent standing and sitting (362), reflecting recall and social desirability bias. Garfield et al (363) conducted the first study that simultaneously evaluated the validity of four physical activity questionnaires (the Baecke questionnaire, the Zutphen Physical Activity Questionnaire, the Stanford 7-day Physical Activity Recall Questionnaire [PAR], and the Physical Activity Scale for the Elderly Questionnaire) against a multi-sensor accelerometer in people with moderate to severe COPD (363). They found that only the score of the PAR was significantly associated with time spent engaging in ≥ 3 METs obtained by a multi-sensor accelerometer ($r = 0.54$; $p < 0.001$) and the PAR also predicted active people (≥ 30 minutes at ≥ 3 METs) (363). However, the PAR cannot accurately measure the amount of physical activity and sedentary behaviour for people, nor can it provide information pertaining to the domain in which the physical activity and sedentary behaviour were performed (363).

Although measures obtained by subjective methods may show inaccuracies because of a long recall time period (364), detailed questioning related to physical activity for recent time periods (i.e. two days) has been shown to increase the reliability of the information gathered from people with COPD (365). The Multimedia Activity Recall for Children and Adults (MARCA) is a computer-based time instrument that, through a structured interview format, records and constructs detailed daily physical activity information (365). The MARCA has been demonstrated to be reliable (intra-class correlation coefficients [ICC] for test-retest ≥ 0.9) (365). This instrument also has been demonstrated to be valid ($r = 0.47$ to 0.80) when compared to two physical activity monitors in people with COPD, for measuring time and energy expenditure associated with physical activities and sedentary behaviours (365). However, it should be noted that that data provided using the MARCA are not as accurate as motion sensors in terms of recording actual movements (365). Despite these limitations, these subjective methods provide detailed information on the type of activities performed during daily life, which can be useful in setting targets and goals for participation in daily physical activity, depending on people's preferences (70). The low cost and simplicity of using subjective methods has led to their widespread use in clinical practice and epidemiological research (70).

2.5.3.2 Objective methods

Objective methods for quantifying physical activity and sedentary behaviour commonly use motion sensors, such as pedometers or accelerometers, to capture body movement (361). The measurement properties of motion sensors and their outcomes differ considerably. Most motion sensors necessitate technical expertise to collect, download, and interpret the data. The selection of a physical activity motion sensor requires careful consideration of the device's cost, validity, reliability, convenience, research and clinical goals, responsiveness and the population being studied (366).

2.5.3.2.1 Pedometers

Pedometers are considered the simplest motion sensors as they are small, inexpensive, and easy to use. Most models are worn on the waist and contain a horizontal spring-suspended lever arm that deflects with the up and down motion (vertical acceleration) of the hips during walking (367). However, one of the limitations of pedometers is that any vertical movement, such as vibrations while seated in a moving car, may trigger the device to count the movement as a step (368). Moreover, pedometers do not provide data related to the pattern of physical activity and sedentary behaviour, nor the intensity of the activities performed (369). Pedometers are often less sensitive to the steps of people who have a slow or shuffling gait, and therefore tend to undercount-steps in the COPD population (370-373). For instance, the study by Furlanetto et al (373) which included people with COPD, found that, compared to steps counted by direct observation, pedometers under-estimated the number of steps at slow speed of 1.4 ± 0.3 km/h (79 ± 17 *versus* 26 ± 26 steps; $p < 0.05$).

Despite the limitations of pedometers, these motion sensors appear to be useful tools for those aiming to optimise their physical activity (374). For example, Mendoza et al (375), whose study included people with mild COPD, reported a 56% increase in steps per day in those people who wore a pedometer for three months and were encouraged to increase their daily physical activity.

2.5.3.2.2 StepWatch™ Activity Monitor

The StepWatch™ Activity Monitor (SAM) (OrthocareInnovations, Seattle, Washington, USA) has the ability to record steps accurately at fast and slow walking speeds (376, 377). This monitor is a small (75 × 50 × 20 mm) microprocessor-linked sensor enclosed within a lightweight (38 g), pager-sized, durable casing. This monitor is worn on the right ankle and secured in place using a Velcro strap and can be covered by clothing. It uses a combination of position, timing, and acceleration to detect steps (378). The SAM has a sampling frequency of 128 Hertz (Hz) and records the number of steps taken every minute (378). This monitor costs approximately $525 AUD and $2500 AUD for the computer interface docking station. Several studies have established the accuracy of the SAM in measuring steps in populations characterised by their slow walking speeds (376, 378). In people with COPD, the SAM has been demonstrated to have an excellent capacity to accurately detect steps, irrespective of walking speed or use of a wheeled-walker, when compared to direct observation (377).

Given the advantages of the SAM and the fact that Saudi nationals tend to wear traditional long dress, the SAM appears to be suitable for use in this population, and therefore the SAM was selected for the study described in Chapter 5 of this thesis.

2.5.3.2.3 Accelerometers

Accelerometers have been developed with increasingly advanced motion sensors that measure the acceleration of body movements in one (uniaxial), two (biaxial) or three (triaxial) planes (379, 380). One of the advantages of most accelerometers is their ability to accurately determine the quantity and intensity of movement over a specific period of time (381). Depending on the type of accelerometer, these monitors can be worn on the waist, hip, wrist, back, and upper or lower limbs. The percentage of time spent active and performing specific activities can be calculated, depending on the type of accelerometer. The output from some accelerometers can be used to divide waking time into sedentary behaviour, and light, moderate and vigorous intensity of physical activity (359). Moreover, some of them have the capacity to distinguish brisk walking from other activities of daily life (382). However, accelerometers are

often more expensive than pedometers and most need technical expertise to collect, download and analyse the data (70).

2.5.3.3 Other methods for measuring physical activity

There are other methods that can be directly and indirectly used to measure physical activity. Direct observation is considered the gold standard method to measure physical activity. It is undertaken by observers who watch or videotape activities performed by people and quantify them (361). However, this method is very time consuming, intrusive and inappropriate for large populations (383).

The assessment of energy expenditure using doubly labelled water is an indirect method used to estimate physical activity. This method is a standard technique for measuring energy expenditure that uses a quantity of water containing both stable oxygen and hydrogen isotopes. This method is based on the principle that after drinking a quantity of oxygen and hydrogen isotopes, oxygen is eliminated as carbon dioxide and water, and deuterium is eliminated from the body as water. The difference between the two isotope elimination rates is used to calculate the total energy of the body (384). The high cost of materials and expertise needed to analyse the isotope concentrations using mass spectrometry limits the use of doubly labelled water as a measurement technique in large population studies (384, 385).

2.5.4 Factors associated with the measurement of physical activity and sedentary behaviour

Generally, the measurement of physical activity and sedentary behaviour appears to be highly variable in amount, intensity and type, and is influenced by many factors related to sampling (386). These factors include the number of hours per day and the number of days of monitoring (387, 388), whether measurements are obtained over weekdays versus weekend days (389) and the impact of seasonal variation (390).

Determining the minimum number of hours per day and number of days of activity monitoring is required to minimise the burden for participants but still reflect the habitual activity of people (387, 391). A review by Masse et al (387) concluded that wearing motion sensors for 10 hours or 60% of waking time a day in the adult population is required to accurately reflect their daily physical activity levels. In the

healthy adult population, habitual level of activity varies considerably, and therefore, three to five days of activity monitoring has been recommended to obtain a measure of physical activity (386, 388). In older populations, it has been found that two valid days of monitoring physical activity are considered the minimum number of required days to assess physical activity (ICC $\geq$ 0.8) (392, 393). This finding is consistent with that reported by Pitta et al (56), who found that measurement for only two weekdays was required to produce an acceptable reliability (ICC $\geq$ 0.7), for the time spent in various body positions (lying down, sitting, standing and walking). However, Watz et al (85) found that at least three days were necessary to reliably (ICC $\geq$ 0.7) measure average daily physical activity in people with mild to severe COPD. These authors found that only two days of physical activity monitoring were required for people with very severe COPD (85). Steele et al (82) found that three days of physical activity monitoring were required to reliably (ICC $\geq$ 0.70) quantify physical activity for those with moderate to severe COPD. Pooling the results of these studies, it would seem that at least three days of physical activity monitoring would be appropriate to adequately measure the average daily activity for people with COPD.

Although most of the studies mentioned above recommended a minimum of three days for monitoring, it is important to determine whether these three days need to be consecutive or whether a combination of any three days of monitoring is acceptable in order to provide a reliable measurement of physical activity. Studies that included healthy adult people have shown that a decrease in physical activity occurred on Sundays when compared to other days of the week (355, 389). However, an earlier study demonstrated less day-to-day variability in physical activity, when measures were collected over seven consecutive days in people with COPD (368). Lorse et al (78) measured physical activity over seven consecutive days using an accelerometer in 23 people with moderate to very severe COPD and found that accelerometer activity counts for people with COPD did not differ between three within-week measurement periods or between weekdays and weekend days ($r > 0.97$; $p < 0.001$) (78). Given the results of these studies, it would appear that a combination of any three days of physical activity measurement are sufficient to accurately quantify physical activity in people with COPD.

Seasonal variation appears to impact on physical activity and sedentary behaviour, with lower levels of physical activity seen during winter than summer ($p = 0.02$) (390). Sewell et al (390) showed that people with COPD who commenced a pulmonary rehabilitation program in winter attained a greater improvement in daily physical activity compared to those who started the program in summer ($p = 0.04$). In line with the influence of seasonal variation, Moy et al (369) demonstrated that people with COPD, who had their baseline measurement of physical activity in winter and follow-up in spring, had an increase in daily steps, whereas those who had their baseline visit in autumn and follow-up in winter experienced a decline in daily steps, after controlling for baseline step count ($p = 0.013$). In Saudi Arabia, data pertaining to the impact of seasonal variation on physical activity and sedentary behaviour are unavailable.

2.5.5 Impact of COPD on physical activity and sedentary behaviour

There is strong evidence demonstrating that people with stable COPD walk less compared with age and gender-matched healthy people (55-58, 76, 78). Specifically, it appears that people with stable COPD walk for a shorter duration and more slowly than their healthy counterparts (55-58). One of the first studies reporting this difference was conducted by Pitta et al (56), who used an accelerometer (DynaPort Activity Monitor) to provide detailed information on time spent in different activities and positions by people with mild to very severe COPD compared with healthy controls. They demonstrated that, compared with healthy controls, during waking hours, people with COPD spent less time standing (191 ± 99 *versus* 295 ± 109 min/day, $p < 0.001$) and walking (44 ± 26 *versus* 81 ± 26 min/day, $p < 0.001$) (56). Vorrink et al (58) reviewed data related to physical activity in people with COPD compared with healthy controls. This review concluded that the proportion of time people with COPD spent engaging in physical activity each day was only 57% of the time spent by healthy controls (58). Furthermore, people with COPD walked around 25% slower than their healthy counterparts (56, 58). Pitta et al (56) found that people with COPD walked at a slower intensity when compared with age and gender matched healthy people (1.8 ± 0.3 versus 2.4 ± 0.5 m/s^2; $p < 0.0001$). These data were similar to that reported by Hernandes et al (57) who demonstrated that people

with COPD walked with lower movement intensity when compared with their healthy controls (1.9 ± 0.4 versus 2.3 ± 0.6 m/s^2; p = 0.004).

There are some data related to the way in which physical activity is accumulated by people with COPD demonstrating that people with COPD walk in short interrupted bouts instead of long continuous walking (394, 395). For example, Pitta et al (394), included 29 people with COPD, demonstrated that before and after pulmonary rehabilitation, time spent in walking in daily life was accumulated in very short bouts (up to one minutes in length). Similarly, Jehn et al (395) found that walking time spent by people with COPD each day was accumulated in short interrupted bouts of less than five minutes.

Besides participating in lower levels of physical activity during waking hours, people with COPD also spend larger proportions of time in sitting and lying positions compared to healthy controls (56). For example, one study found that people with COPD spent 52% and 12% of their waking hours in sitting and lying positions, compared to 42% and 4% in healthy controls (56). These findings indicate that people with COPD participate in less physical activity and spend much of their day in sedentary behaviour, such as sitting or lying down, when compared with healthy people of a similar age and gender.

2.5.6 Factors associated with physical activity and sedentary behaviour in COPD

Dyspnoea and fatigue are frequently reported by people with COPD during daily activities, and the adoption of a sedentary lifestyle by this population is presumably a strategy to minimise these symptoms during daily activities (10, 56). People with COPD who participate in low levels of physical activity are likely to experience deconditioning of both the cardiovascular system (115, 396) and muscles of locomotion (147, 397), which can lead to deterioration in their exercise capacity and HRQoL (398). Several factors have been demonstrated as being associated with low levels of physical activity in COPD, including increased dyspnoea, COPD severity, functional disability and exercise capacity, extrapulmonary manifestations and risks of hospitalisation and mortality (56, 85, 115, 134, 399, 400).

Research has supported the importance of subdividing walking time based on the METs levels defined earlier, showing that time spent engaged in moderate to vigorous physical activity is associated with higher functional exercise capacity and lower all-cause mortality in people with stable COPD (56, 133). Moreover, time spent engaged in light intensity physical activity may decrease the risk of developing cardiovascular diseases and type 2 diabetes in healthy people (359). Further, sedentary behaviour has been identified as a risk factor for metabolic diseases and premature death in the general population (359, 401). Prolonged sedentary behaviour is associated with factors including lower exercise capacity, less autonomous motivation for exercise, use of long term oxygen therapy and a higher number of exacerbations in the past year (59).

2.5.6.1 Dyspnoea

Low levels of physical activity have been associated with dyspnoea in people with COPD (57, 84). For example, a study by Watz et al (85) measured physical activity using a multi-sensor armband, and assessed dyspnoea using the mMRC dyspnoea scale in 163 people with stable COPD. This study showed that those people who reported feeling too breathless to leave the house (mMRC grade 4) were sedentary as they had a low energy expenditure (1.26 METs), which is considered slightly greater than a chair-or bed-bound patient (402). The authors also found that increasing levels of dyspnoea were associated with fewer steps and less time spent in moderate intensity physical activity (> 3 METs) (85). Data pertaining to the relationship between dyspnoea and sedentary behaviour in COPD are lacking.

2.5.6.2 Functional disability and exercise capacity

In people with COPD, low levels of physical activity have been associated with increased functional disability and decreased exercise capacity (399, 403). A population-based cohort study included 206 people with COPD and used the Community Healthy Activities Model Program for Seniors Physical Activity Questionnaire, and the Valued Life Activities scale to measure physical activity and disability, respectively (399). The results of the study demonstrated that a low level of physical activity at baseline was a strong predictor of a prospective increase in disability over the following year (odds ratio [OR] 2.5, 95%; CI 1.1 to 5.3) (399)

A moderate to strong association has been demonstrated between daily physical activity, expressed as walking time, and exercise capacity, measured as the 6MWD ($r > 0.42$, $p < 0.01$) (56, 57). This corroborates the associations demonstrated by Watz et al (85), who showed that the 6MWD had a strong association with the steps accumulated and a moderate association with the number of minutes spent performing moderate intensity physical activity each day ($r = 0.63$ and 0.47 respectively; both $p < 0.001$).

In 113 people with mild to moderate stable COPD, a strong association has been found between functional exercise capacity, measured using the 6MWT, and sitting time ($r = 0.74$, $p < 0.001$), measured using a triaxial accelerometer (DynaPort), indicating that functional limitations increase with prolonged time spent in sedentary behaviour (59).

2.5.6.3 Health related quality of life

Reduced levels of physical activity have been demonstrated to be associated with poor HRQoL in people with COPD (134, 404). Jehn et al (134) demonstrated that the time spent in fast walking (5km/h measured using an accelerometer) was associated with HRQoL, measured using the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) and SGRQ. Specifically, a moderate association was found between the time spent walking at more than 5km/h and the score of the physical function component of the SF-36 ($r = 0.4$, $p < 0.05$). Similarly, a moderate association was demonstrated between the time spent walking at more than 5km/h and the score of the activity domains of the SGRQ ($r = -0.40$, $p < 0.05$) (134). These results suggest that people with COPD who had the lowest daily intensities of physical activity had the worst HRQoL. However, a study by Coronado et al (405) showed no association between physical activity, measured using an accelerometer, and HRQoL, assessed using the SGRQ. This study measured physical activity on the first day and last day of a three-week pulmonary rehabilitation program for 15 people with COPD. The lack of association in this study may be due to their small sample size and a large range seen in the total score of SGRQ (42 ± 11 for the first day and 31 ± 12) for the last day). In addition, walking activity in this study was assessed in the rehabilitation centre environment, which does not reflect a normal pattern of daily activities, whereas the SGRQ assesses HRQoL in the individual's usual

environment. Data pertaining to the association between HRQoL and sedentary behaviour are not available.

2.5.6.4 Disease severity

Although decrements in physical activity have been demonstrated in people with COPD, it appears that these decrements increase with increased disease severity (55, 85, 395, 406). One of the largest early studies, which used a multisensor armband monitor (SenseWear Armband, Bodymedia, Pittsburgh, PA) to investigate physical activity levels in 70 people with stable mild to very severe COPD and in 30 healthy people, showed that daily steps and time spent in moderate activities decreased with increased COPD severity (55). That is, compared to the values obtained in healthy controls, the number of steps per day accumulated by people with COPD was 87% ± 34% for those with mild disease, 71% ± 32% for moderate, 49% ± 34% for severe, and 29% ± 20% for those with very severe disease. The same study showed that the time spent in moderate intensity physical activity (3.6 ≥ METs) was 53% ± 48%, 41% ± 45%, 31% ± 48%, and 22% ± 33% of the values seen in healthy controls for those with mild, moderate, severe and very severe COPD respectively. These differences were statistically significant for those with moderate to very severe COPD when compared with that seen in healthy controls ($p < 0.05$) (55). This finding is consistent with that reported by Jehn et al (395), who used an accelerometer to measure physical activity in 107 people with stable COPD. This study found that the number of steps per day decreased with increasing severity of COPD (moderate: 5075 ± 2753, severe: 4318 ± 2272, very severe: 3189 ± 2238; $p < 0.05$). In addition, Jehn et al (395) demonstrated that daily walking time was accumulated in short, intermittent bouts of less than five minutes. This is consistent with Pitta et al (394), who demonstrated that walking time during daily life accumulated in very short bouts of walking (up to 1 minute in length) before and after pulmonary rehabilitation. In contrast to data on physical activity, Hartman et al (59) demonstrated, using a triaxial accelerometer (DynaPort), that sedentary time accumulated by people (n = 113) with mild to very severe COPD dids not differ across their disease severities.

2.5.6.5 Extrapulmonary manifestations

It appears that reduced physical activity is associated with the presence of extrapulmonary manifestations of COPD (115). Watz et al (115) investigated the associations between the extrapulmonary effects of COPD and decreased levels of physical activity of 170 people with stable COPD, measured using an accelerometer. They found that high levels of left cardiac dysfunction and systemic inflammation, specifically N-terminal pro– B-type natriuretic peptide levels and high-sensitivity C-reactive protein, were associated with decreased physical activity, independent of COPD severity according to the GOLD or the multidimensional BODE index.

Parker et al (407) objectively measured sedentary time using the ActiGraph in 223 people with COPD. The authors demonstrated that no significant differences in sedentary time between those with and without metabolic syndrome. Sedentary time was associated with a large waist circumference and high blood glucose levels (all $r = 0.2$, $p < 0.05$), indicating greater cardio-metabolic risk.

2.5.6.6 Hospitalisation

In people with COPD, low physical activity has been associated with hospitalisation for an AECOPD (408) and mortality (133, 400). A cohort study of 2,386 people with COPD demonstrated that those who reported performing a minimum of two hours walking or cycling a week, measured using a self-reported questionnaire, had a 30% to 40% reduced risk of both hospitalisation due to an AECOPD and mortality over a 20 year period (133). This is similar to the findings of by Benzo et al (408), who showed that less than two hours of physical activity per week, assessed by a self-reported questionnaire, was a significant predictor (OR 0.60, 95%; CI, 0.41 to 0.88) of hospitalisation for an AECOPD in 610 people with COPD. Esteban et al (409) followed 391 people with COPD for more than two years. They showed that those who maintained a low level of physical activity, where physical activity was assessed using a questionnaire, demonstrated an increased rate of hospitalisation for an AECOPD compared to those who were more active (OR 1.90; 95% CI 1.09 to 3.32). This study also found that those who had the highest level of physical activity at baseline and had a reduction in their physical activity during the follow-up period demonstrated an increased rate of hospitalisation (OR 2.134; 95% CI, 1.15 to 3.98).

It has been shown, in 113 people with mild to very severe stable COPD, that prolonged time spent in sitting is associated with a higher number of exacerbations in the past year ($r = 0.31$, $p < 0.05$) (59). It appears that those who had been hospitalised due to an AECOPD experienced a prolonged impact on their physical activity and sedentary behaviour levels. Compared to people with stable COPD, those who were hospitalised for an AECOPD spent more time sitting and less time walking and standing, up to one month following hospital discharge (304).

2.5.6.7 Mortality

A decline in physical activity levels is associated with an increased risk of all-cause mortality in people with COPD (400, 410). The prognostic value of physical activity, measured using an accelerometer, was evaluated in 173 stable people with COPD by Garcia-Rio et al (411). They demonstrated that for every 10 vector magnitude units that daily physical activity increased, the risks of mortality and hospitalisation reduced by 14% and 11%, respectively, after adjusting for relative confounders such as age, gender, Body Mass Index, current smoking, Charlson co-morbidity index, and treatment with long term oxygen therapy or inhaled corticosteroids (411). Waschki et al (400) measured daily physical activity of 170 people with stable COPD using a multi-sensor armband. They demonstrated that physical activity was the best predictor of all causes of mortality (400). The authors demonstrated that every 0.5 SD increase in the number of daily steps (equivalent to 1,845 steps) was associated with a lower risk of death (hazard ratio 0.49, 95% CI, 0.34 to 0.69) after standardisation and adjustment for age and gender (400). Pooling the results of these studies, it appears that regular participation in physical activity reduces the risk of mortality in people with COPD. No data are available for the relationship between sedentary behaviour and mortality in people with COPD.

In summary, people with COPD are characterised by low levels of physical activity, with worsens with increasing dyspnoea and disease severity. In addition, physical activity and sedentary behaviour appear to be associated with lower exercise capacity and disability, and risk of hospitalisation and mortality (only with physical activity level). However, little is known about the impact of sedentary behaviour on health outcomes in people with COPD. In addition, there is there no information about

physical activity and sedentary behaviour in people with COPD in Arabic Gulf countries.

CHAPTER 3

RELIABILITY AND VALIDITY OF AN ARABIC VERSION OF THE DYSPNOEA-12 QUESTIONNAIRE FOR SAUDI NATIONALS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

3.1 Overview

Dyspnoea is a multidimensional and subjective experience of a difficult or uncomfortable sensation of breathing. It originates from an interaction between physiological, psychological, social and environmental factors (412). For people with chronic obstructive pulmonary disease (COPD), dyspnoea is often the most distressing symptom and is frequently the primary reason for seeking medical help (412). The sensation of dyspnoea leads to disability and a negative effect on the health-related quality of life (HRQoL) for those with COPD (221). Dyspnoea is perceived and expressed similarly to pain in terms of its severity, quality of the sensation and the emotional response that it evokes (27, 413). The quality of the sensation may assist in determining the underlying cause of dyspnoea (414). The emotional response to dyspnoea induces distress and is commonly observed in clinical and laboratory settings (31, 228). Increases in the emotional response to the sensation of dyspnoea in people with COPD leads to functional impairment during their activities of daily living and greater reductions in their HRQoL (39). Tools that are commonly used to evaluate perception of dyspnoea in people with COPD at rest or during exertion include the modified Borg scale and visual analogue scales (17, 415). These tools are unidimensional and may not reflect different components of dyspnoea, such as quality of the sensation and emotional response to dyspnoea. A multidimensional tool, the Dyspnoea-12 questionnaire (D-12) was developed to quantify the severity of both the quality of the sensation and the emotional response to dyspnoea, using descriptors associated with various cardiopulmonary diseases (23). The English version of the D-12 has been demonstrated to be reliable and valid in people with pulmonary diseases such as COPD and asthma (23, 40). Further, the

D-12 has been translated into different languages such as Korean and Japanese (43, 44). In Arabic Gulf countries, there is limited work in COPD and that results in a lack of tools used to measure dyspnoea in people with COPD. Therefore, it is important to develop and validate a tool such as the D-12 to assess dyspnoea in an Arabic Gulf COPD population, specifically in Saudi Arabia.

The study presented in this chapter has been published in the Annals of Thoracic Medicine (416). However, additional data pertaining to the reliability of the D-12 obtained for people who were grouped according to their disease severity have been added to this chapter.

3.1.1 Overall aim

The primary aim of this study was to translate the D-12 into the Arabic language and investigate the reliability and validity of an Arabic version of the D-12 in people with COPD. The secondary aim was to explore the reliability of the D-12 for people with COPD grouped according to disease severity.

3.1.2 Research hypotheses

The primary hypothesis for this study was: The D-12 will be reliable and valid in Saudi nationals with COPD.

The secondary hypothesis for study was: The D-12 will be reliable in people with COPD grouped according to disease severity.

3.2 Methodology

This study comprised two parts (A and B). Part A involved translating the D-12 from English into Arabic and part B examined the reliability and validity of the Arabic version of the D-12. The study was approved by the Institutional Review Board at King Fahad Medical City, Saudi Arabia (approval number 12/038) and the Human Research Ethics Committee of Curtin University, Australia (approval number HR 106 /2012). Participants provided written, informed consent prior to data collection.

3.2.1 Participants

3.2.1.1 Recruitment

People with COPD were recruited from the outpatient pulmonary clinics at King Fahad Medical City in Riyadh, Saudi Arabia. During the clinic visit, consecutive patients with COPD were asked by their respiratory physician whether they were interested in being told about the study. Those who expressed an interest were contacted by the primary investigator (MA) who provided all necessary information related to the study. Participants provided written, informed consent prior to data collection.

3.2.1.2 Inclusion criteria

To meet inclusion criteria for both parts of the study, participants needed a spirometric diagnosis of COPD, in accordance with the criteria established by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (10). In addition, participants were required to be clinically stable (defined as no change in medication use over the past four weeks) and to be able to read and write Arabic.

3.2.1.3 Exclusion criteria

For part B, participants were excluded if they had a comorbidity that limited mobility, such as severe musculoskeletal impairment and/or symptomatic cardiovascular disease.

3.2.2 Protocol

3.2.2.1 Part A

This part of the study used a process similar to that described previously for translating questionnaires into a different language (417, 418). First, the English version of the D-12, presented in Appendix A, was translated into Arabic by two independent certified professional translators. Second, these two Arabic versions of the D-12 were reviewed by an expert panel that comprised three respiratory physicians, one respiratory therapist, one respiratory health educator and one physical therapist. The panel compared the two translations with the original D-12

and suggested alternative words for any ambiguous items. A single version of the Arabic D-12 was produced via consensus. Third, the Arabic version of the D-12 was translated back into English by two other independent, certified translators, who were not aware of the original English version. These versions were compared to the original English version to confirm concordance. The comparison of the back translated versions with the original English version was performed by the expert panel and the translators to identify any discrepancy encountered during the translation process. Finally, the Arabic version of the D-12 was presented to five participants with COPD to ensure that all items were easily understood. This was done by asking the five participants to complete the Arabic version of the D-12 and then to answer the following question 'Was each item of this questionnaire easily understood? If not, please determine the item'. In addition, participants were asked to write any comment related to the questionnaire, if they had.

3.2.2.2 Part B

This part of the study was a cross-sectional study with measures collected during two assessment sessions, completed two weeks apart. During the first session, participants completed three questionnaires. Specifically, they completed Arabic versions of the D-12 first. Thereafter, participants performed two six-minute walk tests separated by a 30-minute rest period. During the rest period, the COPD Assessment Test (CAT) (419, 420) and the Chronic Respiratory Disease Questionnaire (CRDQ) were completed (239, 421). Measures were collected of airflow obstruction. Age, gender, weight and height were recorded. During the second assessment session, participants again completed the Arabic version of the D-12. In order to optimise the completeness of the Arabic version of the D-12 on the second assessment, each participant was contacted by telephone both before and after the scheduled second assessment. One week before the second assessment, a copy of the Arabic version of the D-12 was posted to every participant with a reply-paid registered post envelope in which to return the completed questionnaire. Specifically, participants were contacted by the primary investigator (MA) to ensure that they had received the questionnaire. During the same phone call, participants were reminded to complete the questionnaire and asked a standard question to identify whether or not they had experienced a re-exacerbation. The standard question asked was: 'Has

there been any change in your symptoms over the last two weeks that required you to increase your medication use or to visit a doctor or the hospital? Thereafter, a time within 24 hours of the scheduled assessment was arranged to speak with each participant and go through the questionnaire to ensure its completion.

3.2.3 Measurements

3.2.3.1 Dyspnoea

Dyspnoea was measured using the Arabic version of the D-12, which comprises 12 items: seven related to the quality of the sensation of dyspnoea and five related to the emotional response to this sensation. Each item is graded in terms of its severity on a scale of none (score = 0), mild (score = 1), moderate (score = 2), or severe (score = 3). The D-12 produces a total score ranging from 0 to 36, with higher scores indicating greater severity (23).

3.2.3.2 Health status

Health status was measured via the CAT. The CAT consists of eight items and addresses cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitation at home, confidence leaving home, sleep and energy. Each item was scored on a six-point scale, with higher scores indicating poorer health status (419).

3.2.3.3 Disease-specific health-related quality of life

Health-related quality of life was measured using the self-administered CRDQ with the standardised dyspnoea domain (241, 421). This questionnaire consists of 20 items grouped into four domains; dyspnoea, fatigue, emotional function and mastery. Each item was scored on a seven-point scale, with higher scores indicating better HRQoL (241).

3.2.3.4 Lung function

Post-bronchodilator measures of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were obtained using an Easy One Spirometer (NDD Medical Technologies, Massachusetts, USA), according to the guidelines of the American Thoracic Society (422). The spirometer device was calibrated in

accordance with the manufacturer's recommendations. Measures were expressed as a percentage of the predicted values previously established in a local population (423).

3.2.3.5 Functional exercise capacity

Participants performed the 6MWD on a 45-meter straight course within an enclosed corridor, in accordance with the European Respiratory and American Thoracic Societies technical standards (307). To account for improvements resulting from familiarisation with the tests (424), two tests were conducted, separated by 30 minutes of rest, and the best distance was reported as the test result. The 6MWDs were expressed as a percentage of the predicted values previously established in an international sample (425).

3.3 Statistical analyses

3.3.1 Sample size calculations

Sample-size calculations were conducted using published data (23). Specifically, the weakest association reported between D-12 scores and clinical measures was seen with the FEV_1 ($r = 0.30$) (23). Therefore, in order to establish construct validity, a sample size of 44 participants with COPD was required to detect an association of at least this strength between the D-12 and the clinical measures used in this study ($\alpha = 0.05$, $1\text{-}\beta = 0.8$).

3.3.2 Statistical analyses

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS version 21.0, Armonk, NY: IBM Corp, USA). The distribution of the data was examined using the Shapiro–Wilk test. Test–retest reliability of the D-12 was assessed using an intraclass correlation coefficient (ICC) (426). The weighted kappa coefficient was used to determine the concordance of the responses between the first and second administrations of the D-12. The ICC was also used to assess test-retest reliability of the D-12 for participants grouped according to their GOLD grades. Construct validity of the D-12 scores attained at the first administration was assessed by examining the strength of the associations between the D-12 and the CAT, CRDQ, 6MWD, FEV_1 and FVC using Pearson's correlation coefficients. Differences

in the D-12 scores, with participants grouped according to their GOLD grades, were compared using analysis of variance (ANOVA). Data are presented as mean ± standard deviation (SD) unless otherwise stated. A probability (*p*) value less than 0.05 was used to denote statistical significance.

3.4 Results

3.4.1 Participants

From October 2012 to May 2013, sixty-five people with COPD were screened for possible inclusion into the study, of whom 22% (n = 14) did not meet the study criteria. Of these 14 people, seven people (50%) were excluded due to inability to read and write Arabic. Five and two of the 14 people (36%) who were not included because were not clinically stable and had a comorbidity that limited mobility, respectively.

In this study, 78% (n = 51), who met the study criteria, were approached regarding participation. Of these 51 people, a total of 48 participants were recruited (consent rate of 94%). The three people who declined participation did so because of disinterest. Four of the 48 (8%) participants who consented withdrew before the second assessment, two of them because of travelling overseas and one due to personal issues. Ultimately, data from 44 participants were included in the final analysis.

Four (80%) males and one (20%) female with a mean age of 65 ± 10 year and a mean FEV_1 of 1.45 ± 0.61 L (51 ± 19% predicted) participated in part A of the study. Forty participants (33 [82.5%] males) participated in part B of the study (Table 3-1). No participants reported any changes in their symptoms, clinical status or medication use during the study period.

3.4.2 Part A

The back-translated versions of the questionnaire were remarkably similar to the original English version with the exception of a few words. Specifically, for the first back-translated version of the D-12, the words ‘requires’ and ‘work’ for item two in the original English version were back-translated from the final Arabic version to

words ‘needs’ and ‘effort’, respectively, Appendix B. For the second back-translated version of the D-12, the word ‘agitated’ for item 11 in the original English version was back-translated from the final Arabic version to word ‘ nervous’, Appendix C. After the comparison between the back-translated versions with the original English version, both translators agreed that the words that were not identical to those in the original English version had the same meanings and therefor, they could be replaced to be identical to those in the original English version. All participants reported that all items of the Arabic version of the D-12 were easily understood and no comments were reported by the participants. Appendix D presents the Arabic version of D-12.

3.4.3 Part B

3.4.3.1 Reliability

The Arabic version of the D-12 was completed at the two administrations with no missing values. The ICC for the reliability of the D-12 score was 0.94 ($p = 0.01$). The mean D-12 score for the first administration was 22.5 ± 3.7 and 22.2 ± 3.3 at the second administration (mean absolute difference = 0.3 ± 1.7). Figure 3-1 illustrates the mean scores for each item of the D-12 over the two administrations. Excellent agreement in test scores was observed between the two administration times (weighted kappa = 0.83; $p = 0.001$). The ICC for the reliability of the D-12 score with the participants grouped according to their GOLD grades was 0.90 for GOLD grade 2, 0.97 for GOLD grade 3 and 0.85 for GOLD grade 4 (all $p < 0.01$).

3.4.3.2 Validity

Table 3-2 presents the associations between the D-12 total score and its components obtained at the first administration with the CAT, CRDQ domains, FEV_1, FVC and 6MWD. Strong associations ($r \geq 0.6$) were demonstrated between (i) the total score for the D-12 and the CAT, (ii) the score for quality component of the D-12 and the CAT and, (ii) the score for the emotional response component of the D-12 and the emotional function domain of the CRDQ. The mean total scores of the D-12 differed between participants in GOLD grades 2 and 4 (mean difference = 4.6 ± 4.9; $p < 0.01$). Figure 3-2 illustrates the mean D-12 scores for participants grouped according to GOLD grades.

Table 3-1: Characteristics of the participants who completed part B (n = 40).

	all participants (n = 40)		Males participants (n = 33)		Females participants (n = 7)	
Variable	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range
Age, yr	63 ± 9	45 to 80	64 ± 8	45 to 80	57 ± 9	46 to 70
BMI, kg/m^2	28.0 ± 4.7	18.0 to 38.0	27 ± 5	18 to 38	30 ± 5	22 to 36
FEV_1, L	1.33 ± 0.47	0.52 to 2.41	1.31 ± 0.48	0.52 to 2.41	1.42 ± 0.41	0.83 to 2.12
FEV_1, % predicted	47 ± 16	19 to 78	44 ± 15	19 to 69	60 ± 16	34 to 78
FVC, L	2.53 ± 0.60	1.27 to 3.52	2.53 ± 0.58	1.27 to 3.52	2.53 ± 0.50	1.88 to 3.19
FVC, % predicted	72 ± 15	37 to 96	69 ± 14	37 to 96	85 ± 14	61 to 94
FEV_1/FVC, %	53 ± 11	28 to 69	51 ± 11	28 to 69	55 ± 9	44 to 66
D-12 total score	22.4 ± 3.6	14.0 to 28.0	22.8 ± 3.7	13.0 to 29.0	20.7 ± 3.0	16.0 to 26.0
Quality component	13.6 ± 2.7	7.0 to 18.0	13.9 ± 2.8	7.0 to 18.0	12.1 ± 1.9	10.0 to 16.0
Emotional response component	8.9 ± 1.8	5.0 to 13.0	8.9 ± 1.9	6.0 to 14.0	8.6 ± 1.9	5.0 to 11.0
CRDQ total score, ppi	3.7 ± 0.8	1.9 to 5.5	3.6 ± 0.8	1.9 to 5.5	4.1 ± 0.8	2.9 to 4.9
Dyspnea, ppi	3.9 ± 1.0	2.0 to 5.6	3.8 ± 1.0	2.0 to 5.6	4.5 ± 0.9	3.4 to 5.6
Fatigue, ppi	3.3 ± 1.0	1.2 to 5.0	3.2 ± 1.0	1.25 to 4.7	3.9 ± 1.1	2.0 to 5.0
Emotional function, ppi	3.8 ± 1.0	1.8 to 5.7	3.9 ± 1.0	1.9 to 5.7	4.3 ± 1.0	2.7 to 5.5
Mastery, ppi	3.7 ± 1.1	1.0 to 6.7	3.7 ± 1.2	1.0 to 6.7	4.2 ± 1.0	3.0 to 5.7
CAT	19.1 ± 4.8	8.0 to 27.0	19.5 ± 5.1	8.0 to 27.0	17.6 ± 3.0	14.0 to 23.0
6MWD, m	365 ± 78	176 to 481	357 ± 81	176 to 481	407 ± 47	343 to 480
6MWD, % predicted	68 ± 14	36 to 89	66 ± 14	36 to 89	77 ± 7	67 to 88
GOLD grades						
2	18 (45)		13 (39)		5 (71)	
3	15 (38)		13 (39)		2 (29)	
4	7 (17)		7 (22)		0 (0)	

Data are expressed as mean ± standard deviation (SD) or number (%). BMI: body mass index; CAT: COPD Assessment Test; CRDQ: Chronic Respiratory Disease Questionnaire; D-12: Dyspnoea-12; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease (2: moderate, 3: severe and 4: very severe); kg: kilograms; L: liters; m: meters; ppi: points per item, 6MWD: six-minute walk distance; yr: year.

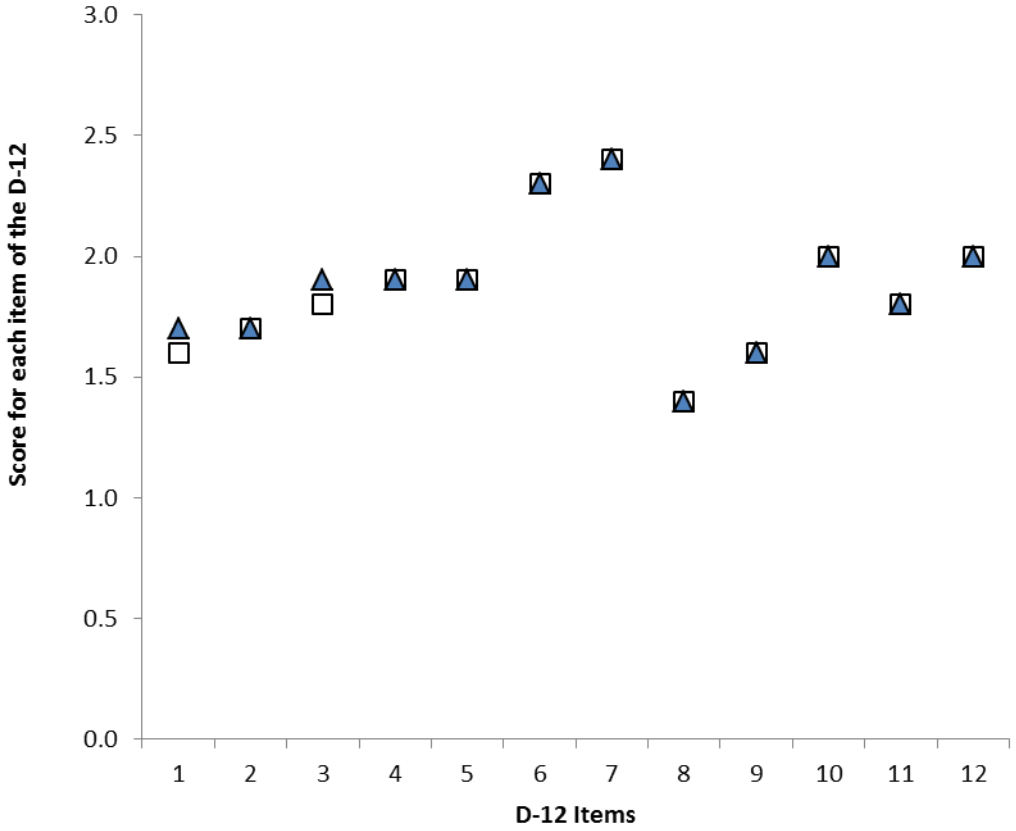

Figure 3-1: Mean scores obtained for each item of the Dyspnoea-12 questionnaire (D-12) on the first administration (closed triangles) and second administration (open squares). On both administration points, the mean scores for items 2, 4, 5, 6, 7, 8, 9, 10, 11 and 12 were identical

Table 3-2: Associations between the D-12 scores from the first administration and CAT, CRDQ, FEV_1, FVC and 6MWD conducted on the same day

	D-12 total score	D-12 quality component score	D-12 emotional response component score
CAT	0.67**	0.61**	0.45**
CRDQ			
Dyspnoea, ppi	–0.56**	–0.55**	–0.31*
Fatigue, ppi	–0.24	–0.03	–0.43**
Emotional function, ppi	–0.39*	–0.07	–0.67**
Mastery, ppi	–0.38*	–0.24	–0.40**
Total, ppi	–0.50**	–0.28	–0.58**
FEV_1, L	–0.38*	–0.57**	–0.09
FVC, L	–0.21	–0.39*	–0.16
6MWD, m	–0.40*	–0.56**	–0.04

CAT: COPD Assessment Test; CRDQ: Chronic Respiratory Disease Questionnaire; D-12: Dyspnoea-12; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; L: liters; m: meters; ppi: points per item; 6MWD; six-minute walk distance. **$p < 0.01$; *$p < 0.05$

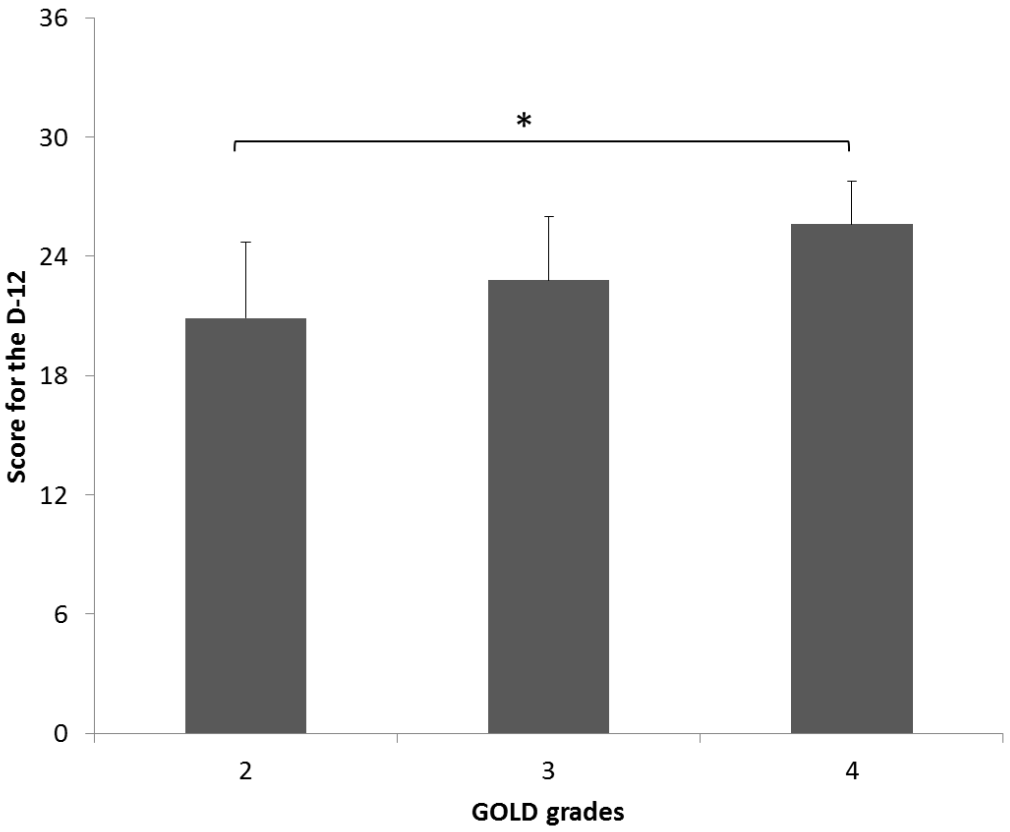

Figure 3-2: Total score for the Dyspnoea-12 questionnaire with participants grouped according to their disease severity, using grades defined by the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD). Data are mean and standard error, calculated from the first administration. ****Statistically significant difference* **($p < 0.05$).**

3.5 Discussion

This study successfully translated the D-12 into the Arabic language and demonstrated that the Arabic version of this questionnaire was reliable and valid in a population of Saudi nationals with COPD. This is consistent with earlier work that has translated questionnaires from English into the Arabic language (420, 421). Although the D-12 is likely to be useful in clinical practice for assessing dyspnoea, in terms of its severity, quality of sensation and emotional response to dyspnoea, further work is required to determine whether this questionnaire is responsive to interventions aimed at reducing dyspnoea, such as the use of bronchodilators and pulmonary rehabilitation. The Arabic version of the D-12 could be used in Arabic speaking people with COPD in more than 22 countries of the Middle East.

Using the methodology previously described to translate the English version of the CRDQ and the CAT into different languages (417, 418), the D-12 was translated into the Arabic language. The back-translation demonstrated good concordance with the original English version and the Arabic version was easily understood. Similar results were found in a study that translated the D-12 into Korean (427).

The D-12 scores obtained in this study were reliable over a two-week period, as demonstrated by the high ICC value and the excellent weighted kappa score. In addition, the scores obtained on the D-12 for people who were grouped according to GOLD grades were reliable, as indicated by the ICC values ≥ 0.85 for GOLD grades 2 to 4. It is noteworthy that the mean scores for 10 of the D-12 items were no different between the two administrations and the mean score for the remaining two D-12 items differed by less than one point. In this study, there were no missing data over the two administration points for the D-12, demonstrating evidence of its utility. In the present study, the ICC value was similar to those values reported in earlier work in which the D-12 was administered twice over the same period in populations with COPD (ICC = 0.90), asthma (r = 0.93 to 0.96) and interstitial lung disease (ICC = 0.94) (23, 40, 428). The high ICC value indicates that the D-12 provides a stable measure of dyspnoea in people with moderate to very severe COPD, which serves to increase confidence that any change in scores following an intervention is unlikely to simply reflect variability in responses to the questionnaire items.

Construct validity was demonstrated as the D-12 total score and its components scores associated significantly and in the expected direction with questionnaire-based assessments. Specifically, data from this study revealed a moderate to strong relationship between the D-12 total score and both the CAT score and the CRDQ total score. In addition, significant relationships were demonstrated with the scores of components of the D-12 and both the CAT and many of the domains of the CRDQ. Earlier work in people with COPD has used the Medical Research Council dyspnoea scale and the Hospital Anxiety and Depression Scale to examine construct validity of the D-12 (23). In contrast, we chose to use the CAT and the CRDQ to establish validity of the Arabic version of the D-12, as both have been validated in the Arabic language (420, 421) and comprise items related to the impact of dyspnoea on the daily life of people. Despite the different questionnaires used, our data were consistent with a previous study in people with COPD (23), showing that scores for the D-12 were associated with dyspnoea during daily life as well as emotional function. Further, the strong association between the D-12 total score and the CAT is consistent with data obtained in adults with asthma, interstitial lung disease and pulmonary hypertension (40, 428, 429) showing a strong relationship between the D-12 total score and a measure of health status. Our data confirm that in Saudi nationals with COPD the perception of dyspnoea contributes significantly to health status and mood.

Associations of weak to moderate strength were demonstrated between the total score of the D-12 and both the 6MWD and the FEV_1. This is consistent with earlier work undertaken in people with COPD (23) and asthma (40), and suggests that dyspnoea worsens with increased functional limitation and disease severity. It is noteworthy that the association between the D-12 total score and both the 6MWD and FEV_1 appears to be driven by the score from the quality component of the questionnaire rather than the score from the emotional response component. This indicates that as COPD increases in severity, people experience a greater severity of various types of dyspnoea sensation, but the emotional response shows a less consistent response pattern. This highlights the value of using a multi-dimensional tool to quantify dyspnoea in this population.

There is lack of tools available to measure dyspnoea in the Arabic speaking populations, in people with COPD or other respiratory diseases. The D-12 focuses on distress associated with dyspnoea as oppose to the tools that are available in the Arabic language, such as the CRDQ and CAT, which they form a part of HRQoL or health status measures only (241, 419-421). Although the CRDQ has a dyspnoea domain, this domain only measures dyspnoea related to specific daily activities and provides no direct measure to dyspnoea sensation in terms of the quality and emotional response to this sensation. The other tool that is available to use in the Arabic COPD population is the CAT (420). However, this tool measures health status and is not designed to measure dyspnoea. People with COPD can be extremely sensitive to dyspnoea, which they may find emotionally overwhelming. Approximately 50% of people with COPD have been found to have anxiety and depression (430). Emotional distress is linked to the severity of dyspnoea. The brain structures involved in the perception of dyspnea have been identified using brain-imaging techniques (431). These images demonstrate evidence for the activation of emotional and cognitive structures similar to that found in other unpleasant experiences. Therefore, emotions appear to play an important role in a person's perception of, and reaction to, dyspnoea. Using the D-12 in the Arabic populations will provide health practitioners and researchers with information about the experience of dyspnoea sensation in terms of the quality and the emotional response to this sensation. This may lead to greater advocacy for programs such as pulmonary rehabilitation which aim to reduce dyspnoea in people with COPD. In addition, the use of D-12 will allow researchers from Arabic speaking countries to compare the experience of dyspnoea of their populations with others such as Western populations.

The mean scores reported by males and females for the quality and the emotional response of the D-12 appear to be similar. This indicates that both genders experienced a similar quality of dyspnoea sensation as well as the same emotional response to dyspnoea. In the present study, it is noteworthy that 50% of people who did not meet the study criteria were illiterate. Therefore, this highlights the importance of developing an interviewer-administered version of the D-12 in order to increase its utilisation for assessing dyspnoea in COPD population.

3.6 Limitations

There are limitations to this study. The size of the sample might be seen as a limitation, the present study used an adequate statistical power and the highly significant statistical results clearly show that it was possible to assess the reliability and the validity of the D-12 with the sample. The participants were only recruited from one centre and included a small proportion of female participants. However, the proportion of females in the sample (7 out of 40 participants; 17.5%) is not profound as the overall prevalence of COPD in females (1.0%) is lower than that reported in males (3.5%) (22.2%) in Saudi Arabia (432). In addition to the study limitations, all participants had a diagnosis of COPD. These factors may limit the generalisability of our results. Further studies with a large sample size, including females, from different regions in Saudi Arabia are needed to increase the generalizability for using the Arabic version of the D-12 in clinical and research settings. Further studies are also required to investigate the responsiveness of the Arabic version of the D-12 to therapeutic interventions, such as pulmonary rehabilitation, or in response to a change in clinical status such as recovery following an acute exacerbation of COPD.

3.7 Conclusions

The Arabic language version of the D-12 is a reliable and valid instrument for assessing dyspnoea in Saudi nationals with COPD and is likely to be a useful tool for assessing dyspnoea in research and clinical settings.

CHAPTER 4

CHANGES IN THE DYSPNOEA-12 QUESTIONNAIRE FOLLOWING AN ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

4.1 Overview

An acute exacerbation of COPD (AECOPD) is an event characterised by a worsening of respiratory symptoms that is beyond the normal day-to-day variations and results in a change in medication of people with COPD (10). Dyspnoea is often the most distressing sensation and the primary reason people with COPD seek medical care (25). Following an AECOPD, some people remain dyspnoeic for up to 60 days (24), which may contribute to a greater activity limitations and poor perceived health status (92).

The Dyspnoea-12 questionnaire (D-12), is a self-reported outcome measure that was developed using 12 descriptors of dyspnoea and is relevant to people with a variety of cardiopulmonary disease, including COPD (23). This questionnaire measures the severity of dyspnoea, incorporating two components; the quality of the sensation and the emotional response to the sensation (23). The D-12 has been demonstrated to be reliable and valid in people with COPD (23). However, the capacity of the components of the D-12 to change in response to an intervention or clinical event that changes dyspnoea has not been determined. Data demonstrating the responsiveness of the D-12 are important to optimise its utilisation in both the clinical and research setting.

4.1.1 Overall aim

The primary aim of this study was to determine whether the quality and emotional response components of the D-12 differed between a period when people were hospitalised with an AECOPD and when they had reached a period of clinical stability following hospital discharge.

The secondary aim was to determine whether the quality and emotional response components of the D-12 discriminated between people with COPD, grouped according to disease severity, during an AECOPD and when they were clinically stable.

4.2 Methodology

4.2.1 Study design

A longitudinal observational study was conducted during which data for each participant were collected every 14 days after hospitalisation for an AECOPD for a total of 98 days. Data collection was undertaken between January 2013 and March 2014 at King Fahad Medical City in Riyadh, Saudi Arabia. This study received approval from the Institutional Review Board at King Fahad Medical City, Saudi Arabia (approval number 12/281E) and the Human Research Ethics Committee of Curtin University, Australia (approval number HR 14/2013).

4.2.2 Participants

4.2.2.1 Recruitment

Participants with a severe AECOPD, defined as an AECOPD which required hospitalisation (10), who were hospitalised within the respiratory ward of King Fahad Medical City were identified by their respiratory physician. Within 24 hours of admission, consecutive people with AECOPD were asked by their respiratory physician whether they were interested in being told about the study. Those who expressed an interest were contacted by the primary investigator (MA), who provided them with all required information related to the study. Written, informed consent was obtained from all participants prior to data collection.

4.2.2.2 Inclusion criteria

The inclusion criteria comprised participants with a diagnosis of moderate to very severe COPD, defined as a post-bronchodilator FEV_1/ forced vital capacity (FVC) < 0.7 and an FEV_1 of < 80% of the predicted value in a healthy adult (i.e. grades 2 to 4 of the Global Initiative for Chronic Obstructive Lung Disease [GOLD]) (10).

4.2.2.3 Exclusion criteria

Participants were excluded from the study if they had; (i) a severe psychotic disorder documented in their medical record; (ii) a severe cognitive disorder documented in their medical record; (iii) an inability to read and write in the Arabic language and/or (iv) no home phone or mobile to enable contact post-discharge.

4.2.3 Protocol

Participants with an AECOPD completed a set of questionnaires within 24 hours of hospitalisation. Specifically, they completed Arabic versions of the D-12 (416), the Chronic Respiratory Disease Questionnaire (CRDQ) (239, 421) and the COPD Assessment Test (CAT) (419, 420). The participants again completed the D-12, CRDQ and CAT on days 14, 28, 42, 56, 70, 84 and 98 after hospital admission. This resulted in a total of eight administrations for each questionnaire. A follow-up-interval of 14 days was selected as the recall period for the CRDQ is 14 days (24, 25). Monitoring participants every 14 days allowed the trajectory of symptom recovery to be examined. Post-bronchodilator spirometry was performed for participants within 24 hours prior to discharge from the hospital.

To optimise the completeness and accuracy of response to all questionnaires completed after hospital discharge, each participant was contacted by telephone both before and after each scheduled follow-up assessment. Specifically, one week before each follow-up assessment, the participants were posted a copy of the questionnaires with a reply-paid registered post envelope in which to return the completed questionnaires. Further, they were contacted to ensure that they had received the questionnaires. During the same phone call, participants were reminded to complete all questionnaires and asked a standard question to determine whether or not they had experienced a re-exacerbation. The standard question asked was: ‘Has there been any change in your symptoms over the last two weeks that required you to increase your medication use or to visit a doctor or the hospital?’ Thereafter, a time within 24 hours of each follow-up assessment was arranged to speak with each participant and go through each questionnaire to ensure their completion.

4.2.4 Measurements

4.2.4.1 Dyspnoea

Dyspnoea was quantified using the D-12, which consists of 12 items that assess dyspnoea severity. Of these 12 items, seven items pertain to the quality of the sensation of dyspnoea and five items relate to the emotional response to this sensation (23). Each descriptor item is rated in terms of its intensity using a scale ranging from none (score = 0) to severe (score = 3). The D-12 provides a total score from 0 to 36, with higher scores representing greater severity of dyspnoea (23). This questionnaire has been demonstrated to be reliable and valid in COPD (23, 416). It is available in the Arabic language (see Chapter 3) (416).

4.2.4.2 Disease-specific health-related quality of life

The self-administered CRDQ with the standardised dyspnoea domain was used to measure HRQoL (241). The CRDQ comprises 20 items grouped into four domains; dyspnoea (five items), fatigue (four items), emotional function (seven items) and mastery (four items). Each item was rated using a seven-point Likert scale, with higher scores representing better HRQoL (241). The standardised dyspnoea domain within the CRDQ includes a list of five standard activities. Respondents were asked to rate how much shortness of breath they had experienced while performing each of the five standards activities. This questionnaire has been demonstrated to be reliable, valid and responsive in COPD (241, 433-435). It is available in the Arabic language (421).

4.2.4.3 Health status

Health status was measured using the CAT. The CAT comprises eight items that assess cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitation at home, confidence leaving the home, sleep and energy. Each item is rated on a six-point scale, with higher scores representing poorer health status (419). The scores of CAT are categorised into severity bands: low impact (CAT scores 1 to 10), medium impact (11 to 20), high impact (21 to 30) and very high impact (31 to 40) (436). The CAT has been demonstrated to be reliable, valid and responsive in COPD (437). It is available in the Arabic language (420).

4.2.4.4 Lung function

Post-bronchodilator FEV_1 and FVC were measured using an Easy One Spirometer (NDD Medical Technologies, Massachusetts, USA), in accordance with the guidelines of the American Thoracic Society (422). The spirometer was calibrated according to the manufacturer's recommendations. Measures were expressed as a percentage of the predicted values established in a local population (423).

4.3 Statistical analyses

4.3.1 Sample size calculations

In clinically stable people with COPD, a previous study demonstrated a difference of 2.73 ± 9.97 points between two administrations of the D-12 conducted 16 days (median) apart (438). As dyspnoea dramatically increases during an AECOPD (24), a difference in the D-12 scores between the period of hospitalisation for an AECOPD and return to clinical stability was expected to be at least double this difference previously reported between repeated administrations. Therefore, sample size calculations were performed to ensure adequate power ($1-\beta = 0.8$, $\alpha = 0.05$) to detect a difference of 5.46 ± 9.97 points in the scores of D-12 between periods of an AECOPD and clinical stability. To detect this change, a minimum of 28 participants were required.

4.3.2 Data management

4.3.2.1 Criteria used to define clinical stability

Changes were explored in both the quality and emotional response components of the D-12 between the first administration in hospital and the time period during the 98 days follow-up when the participants were deemed to have returned to clinical stability. For this purpose, clinical stability was defined as when the change in the score of the dyspnoea domain of the CRDQ between consecutive administrations was neither statistically significant nor clinically important (i.e. change was < 0.5 points per item [ppi] (245).

The duration of the follow-up period, being 98 days, was chosen for this study as earlier work has reported that, following a moderate to severe AECOPD, the severity

of dyspnoea returns to pre-exacerbation levels by 91 days for more than 80% of people with COPD (24, 25).

4.3.3 Statistical analyses

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS version 21.0, Armonk, NY: IBM Corp, USA). The assumption of normality was assessed by graphical (frequency histograms and box plots) and statistical methods (Shapiro-Wilk test). Data that did not follow a normal distribution were analysed using non-parametric statistical tests. All data are expressed as either mean ± SD or median (interquartile range [IQR]). A p value ≤ 0.05 was considered statistically significant.

4.3.3.1 Establishing clinical stability

A one-way repeated measured analysis of variance (ANOVA) was used to compare the scores of the CRDQ, D-12 and CAT at each administration over the 98 days follow-up. To determine the scores for the CRDQ, D-12 and CAT during the period of clinical stability, the scores obtained for each questionnaire between consecutive administrations that were not statistically significantly different were averaged.

4.3.3.2 Comparing measures between AECOPD and clinical stability

Comparisons of continuous data obtained between the first administration in hospital and when the participants had returned to clinical stability were performed using either paired *t*-tests or Wilcoxon tests for parametric and non-parametric data respectively.

To compare changes in the scores of the D-12 components with changes in other questionnaires, the effect size for each questionnaire was calculated as the mean difference in the scores reported during the first administration in hospital and when clinical stability was achieved, divided by the SD obtained at the first administration (439). This method for calculating the effect size has been widely used in studies measuring the responsiveness of the CAT and CRDQ in COPD populations (437, 440, 441) . The strength of the effect size was classified using Cohen's d effect sizes with, > 0.2 being small, > 0.5 moderate and > 0.8 large (442).

4.3.3.3 Sub-analyses to explore the confounding effect of re-exacerbation

In a sub-analysis, those who had re-exacerbated during the follow-up period were excluded from the analysis to determine whether or not including them in the original analyses had impacted on the effect sizes of the questionnaires.

4.3.3.4 Exploring the capacity of the Dyspnoea-12 questionnaire to discriminate between participants, grouped according to disease severity

Total scores as well as scores for the quality and emotional response components of the D-12 were compared between participants grouped according to the GOLD grades and compared using ANOVA.

4.4 Results

4.4.1 Participants

Sixty people were hospitalised for an AECOPD and were screened for possible inclusion in the study. Ten people (48%) were excluded because they did not have home phone or mobile to enable contact post-discharge and were not able to read and write Arabic. Eight (38%) and three (14%) of the 21 people were not included due to their inability to read and write Arabic and a severe cognitive disorder, respectively.

Thirty-nine (65%) were deemed eligible and approached to participate. Of these 39 people, a total of 31 participants were recruited (consent rate of 79%). The eight people who declined participation did so because of lack of interest. Two of the 31 (6%) participants who consented withdrew before they were discharged from the hospital due to personal issues. Ultimately, data from 29 participants were included in the final analysis. Baseline characteristics of the participants are presented in Table 4-1.

Table 4-1: Characteristics of the study participants (n = 29)

	All participants (n = 29)		Males participants (n = 25)		Females participants (n = 4)	
Variable	**Mean ± SD**		**Mean ± SD**		**Mean ± SD**	
Age (yr)	64.9 ± 3.9		64.1 ± 3.8		65.7 ± 4.8	
BMI ($kg \cdot m^{-2}$)	27.8 ± 2.4		27.6 ± 2.5		28.5 ± 1.3	
Smoking (pack/yr)	50.5 ± 15.9		47.0 ± 16.7		50.3 ± 11.5	
FEV_1 (L)	1.11 ± 0.28		1.15 ± 0.29		1.27 ± 0.27	
FEV_1 (%pred)	40 ± 11		40 ± 10		54 ± 8	
FVC (L)	2.30 ± 0.43		2.28 ± 0.44		2.57 ± 0.24	
FVC (%pred)	65 ± 13		63 ± 11		86 ± 7	
FEV_1/FVC (%)	49 ± 9		51 ± 9		49 ± 9	
D-12 total score	27.3 ± 2.2		26.4 ± 3.1		25.5 ± 3.0	
Quality component	15.9 ± 1.5		15.4 ± 2.3		15.0 ± 1.9	
Emotional response component	11.4 ± 1.4		10.9 ± 1.6		10.0 ± 1.6	
CRDQ-dyspnoea domain score (ppi)	2.8 ± 0.4		2.7 ± 0.4		2.9 ± 0.2	
CAT score	26.3 ± 2.0		26.6 ± 1.9		24.3 ± 1.5	
	n	**%**	**n**	**%**	**n**	**%**
Smoking status						
Current smoker	20	69	16	64	4	100
Ex-smoker	8	28	4	16	0	0
Never smoked	1	3	1	4	0	0
Medication during exacerbation						
Bronchodilators (long and short acting)	29	100	25	100	4	100
Inhaled corticosteroids	22	76	20	80	2	50
Systemic corticosteroids	15	52	12	48	3	75
Oxygen therapy	6	41	5	20	1	25
Antibiotics	22	76	18	72	4	100
GOLD grades						
2	5	17	5	20	0	0
3	18	62	15	60	3	15
4	6	20	5	20	1	25
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Length of hospital stay	6	4-9	6	6-8	7	6-9

Data are expressed as mean ± standard deviation (SD) or number (%) or median interquartile range (IQR). BMI: body mass index; CAT: COPD assessment test; CRDQ: Chronic Respiratory Disease Questionnaire; D-12: Dyspnoea-12; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease (2: moderate, 3: severe and 4: very severe); kg: kilograms; L: liters; m: meters; ppi: points per item.

4.4.2 Clinical stability following AECOPD

The sample met the criteria for clinical stability 70 days after the first administration of the questionnaires in hospital. This was because the score of the dyspnoea domain of the CRDQ completed 70, 84, 98 days after the first administration in hospital did not differ statistically from each other and the magnitude of the difference was below the threshold for clinical importance (< 0.5 ppi) (mean scores 3.7 ± 0.6, 3.7 ± 0.7 and 3.7 ± 0.7 ppi respectively, $p > 0.05$) (Figure 4-1).

4.4.3 Changes between AECOPD and clinical stability

4.4.3.1 Dyspnoea-12

Figure 4-2 displays the total scores for the D-12 as well as the scores for the quality and emotional response components of the D-12 reported over the 98 days follow-up. Compared with the scores found during the first administration in hospital, when the group had returned to clinical stability there was a decrease (i.e. improvement) for the total score of the D-12 (26.3 ± 3.0 *versus* 20.1 ± 2.9; $p < 0.001$), the quality component (15.3 ± 2.2 *versus* 11.8 ± 1.5; $p < 0.001$) and the emotional response (11.0 ± 2.0 *versus* 8.3 ± 1.6; $p < 0.001$) (Table 4-2).

4.4.3.2 Chronic Respiratory Disease Questionnaire

Figure 4-1 illustrates the scores for the dyspnoea domain of the CRDQ over the 98 days follow-up. Compared with the scores reported during the first administration in hospital, when the group had returned to clinical stability there was an increase (i.e. improvement) in the scores for the dyspnoea domain of the CRDQ (2.7 ± 0.4 *versus* 3.7 ± 0.7; $p < 0.001$), (Table 4-2). Scores for the fatigue, emotional function and mastery domains of the CRDQ are presented in **Error! Reference source not found.**.

4.4.3.3 COPD assessment tool

Figure 4-3 shows the scores for the CAT over the 98 days follow-up. Compared with the scores reported during the first administration in hospital, when the group had

returned to clinical stability there was a decrease (i.e. improvement) in the scores for the CAT (26.2 ± 2.0 *versus* 20.2 ± 3.9; $p < 0.001$) (Table 4-2).

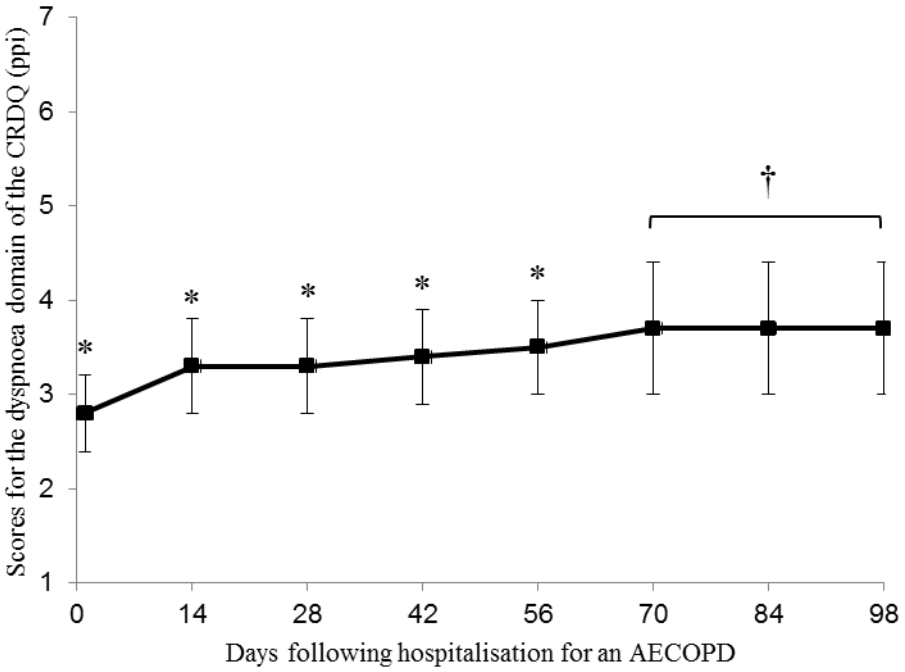

Figure 4-1: Scores for the dyspnoea domain of the Chronic Respiratory Disease Questionnaire during the study period. Data are mean and standard error. ****Statistically significant difference* **($p < 0.05$) from the final administration (day 98). † No significant difference in the score across administrations on days 70, 84 and 98. Therefore, participants were considered clinically stable across these administrations and, for all questionnaires, scores obtained across these last three time points were averaged and used as the score obtained during a period of clinical stability.**

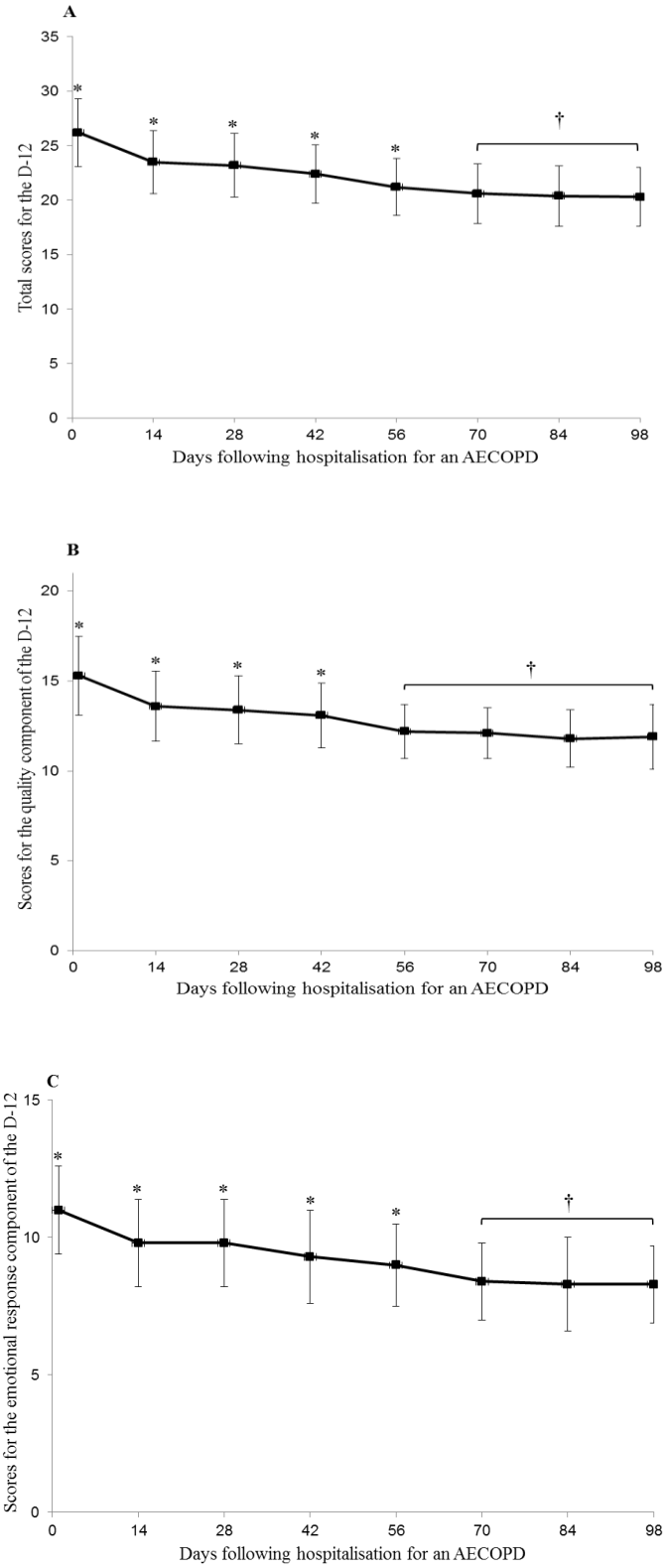

Figure 4-2: A) the total scores of the Dyspnoea-12 questionnaire, B) the score for the quality component of the Dyspnoea-12 questionnaire and C) the score for the emotional response component of the Dyspnoea-12 questionnaire. Data are mean and standard error. ****Statistically significant difference* **($p < 0.05$) from the final administration (day 98). † No significant difference in the scores across administrations.**

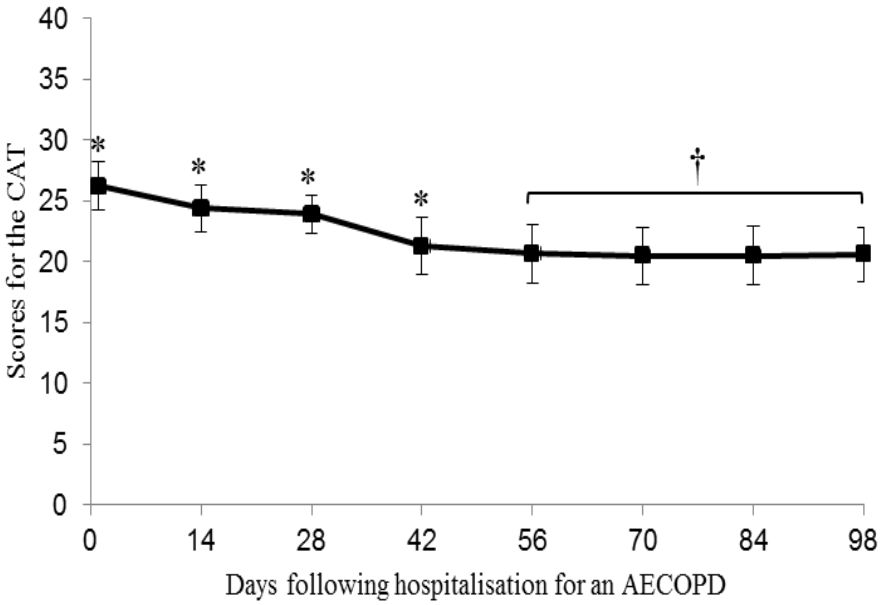

Figure 4-3: Scores of COPD Assessment Test during the study period. Data are mean and standard error. ****Statistically significant difference* **($p < 0.05$) from the final administration (day 98). † No significant difference in the score across administrations 56, 70, 84 and 98.**

Table 4-2: Scores obtained for the D-12, the dyspnoea domain of the CRDQ and CAT during periods of an AECOPD and clinical stability for the group

Variable (n = 29)	First administration (AECOPD) *mean ± SD*	Clinical stability *mean ± SD*	Mean change *mean ± SD*	*p value*	Effect size
D-12 total score	26.3 ± 3.0	20.1 ± 2.9	6.2 ± 2.5	< *0.001**	2.1
Quality component score	15.3 ± 2.2	11.8 ± 1.5	3.5 ± 1.6	< *0.001**	1.6
Emotional response component score	11.0 ± 1.6	8.3 ± 1.6	2.7 ± 1.2	< *0.001**	1.7
CRDQ-dyspnoea score (ppi)	2.7 ± 0.4	3.7 ± 0.7	1.0 ± 0.6	< *0.001**	2.5
CAT score	26.2 ± 2.0	20.2 ± 3.0	6.0 ± 2.9	< *0.001**	3.0

Abbreviations: AECOPD: acute exacerbation of COPD; CAT: COPD Assessment Test; CRDQ: Chronic Respiratory Disease Questionnaire; D-12: Dyspnoea-12; ppi: points per item; SD: standard deviation. **Statistically significant difference.*.

4.4.4 Sub-analyses after removal of participants with re-exacerbation

4.4.4.1 Clinical stability following an AECOPD for participants who did not have re-exacerbations

During the follow-up period, 22 (76%) of the 29 participants (FEV_1% predicted, 44 ± 10) had no further exacerbations during the follow-up period. The remaining seven participants experienced a further exacerbation during the follow-up period. Six of these seven participants experienced only one exacerbation: five out of these six participants had experienced a mild AECOPD (10) and one had experienced a severe AECOPD. Only one participant experienced two exacerbations which were classified as a mild and severe AECOPD. Participants who had a mild AECOPD were managed at home by increasing their medication use. Those who had a severe AECOPD were hospitalised for a period between four to six days.

The participants who did not have re-exacerbations met the criteria for clinical stability 70 days after the first administration of the questionnaires in hospital. That is, the score of the dyspnoea domain of the CRDQ completed 70, 84, 98 days after the first administration in hospital did not differ statistically from each other and the magnitude of the difference was below the threshold for clinical importance (< 0.5 ppi) (mean scores of 3.9 ± 0.6, 3.9 ± 0.6 and 4.0 ± 6 ppi respectively, $p > 0.05$) (Figure 4-4).

4.4.4.2 Changes between AECOPD and clinical stability for participants who did not have re-exacerbations

4.4.4.2.1 Dyspnoea-12

Figure 4-5 shows the total score for the D-12 as well as the scores for the quality and emotional response components of the D-12 reported by the participant who did not have re-exacerbations over the 98 days follow-up. Compared with the scores reported during the first administration in hospital, when the group had returned to clinical stability there was a decrease (i.e. improvement) for the total score of the D-12 (25.1 ± 2.6 *versus* 19.0 ± 1.9; $p < 0.001$), the quality component (14.9 ± 2.3 *versus* 11.0 ± 1.4; $p < 0.001$) and the emotional response component (10.2 ± 1.1 *versus* 8.0 ± 1.0; $p < 0.001$) (Table 4-3).

4.4.4.2.2 Chronic Respiratory Disease Questionnaire

Figure 4-4 demonstrates the scores for the dyspnoea domain of the CRDQ over the 98 days follow-up. Compared with the scores reported during the first administration in hospital, when the group had returned to clinical stability there was an increase (i.e. improvement) in the scores for the dyspnoea domain of the CRDQ (2.8 ± 0.4 *versus* 3.9 ± 0.6; $p < 0.001$), (Table 4-3). Scores for the fatigue, emotional function and mastery domains of the CRDQ are presented in **Error! Reference source not found.**.

4.4.4.2.3 COPD assessment tool

Figure 4-6 illustrates the scores for the CAT over the 98 days follow-up. Compared with the scores reported during the first administration in hospital, when the group had returned to clinical stability there was a decrease (i.e. improvement) in the scores for the CAT (26.1 ± 1.9 *versus* 19.4 ± 2.2; $p < 0.001$) (Table 4-3).

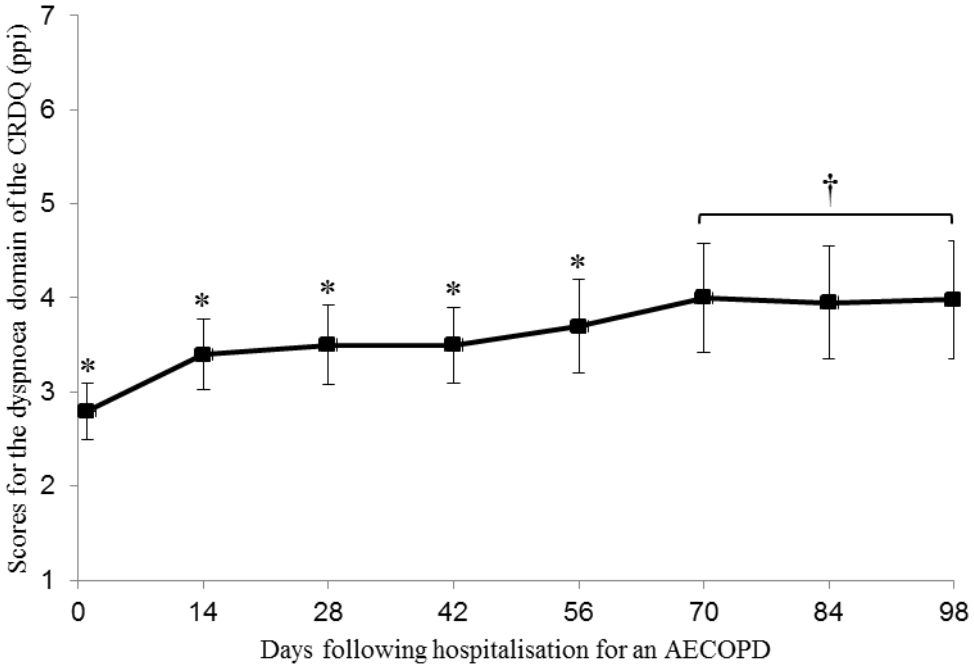

Figure 4-4: Scores for the dyspnoea domain of the Chronic Respiratory Disease Questionnaire for the participant who did not have re-exacerbations during the study period. Data are mean and standard error. ****Statistically significant difference* **($p < 0.05$) from the final administration (day 98). † No significant difference in the score across administrations on days 70, 84 and 98. Therefore, participants were considered clinically stable across these administrations and, for all questionnaires, scores obtained across these last three time points were averaged and used as the score obtained during a period of clinical stability.**

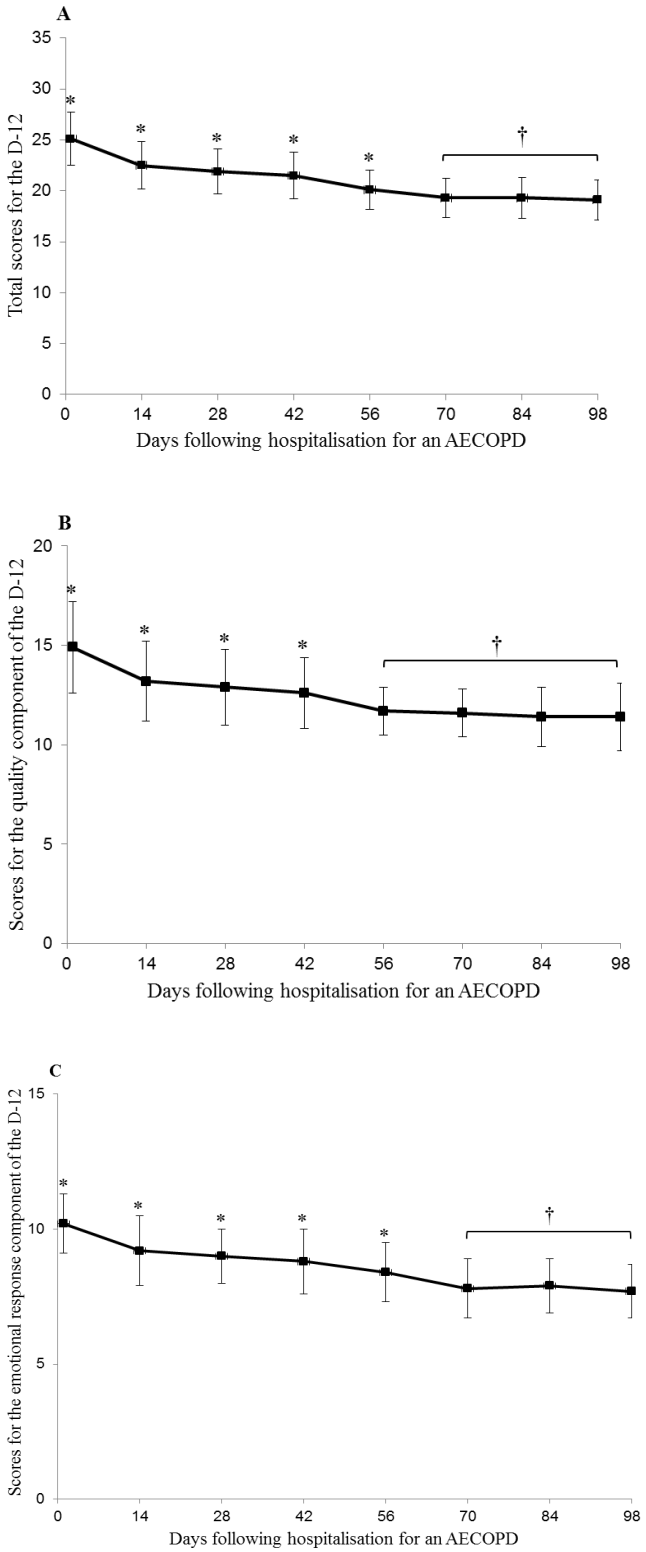

Figure 4-5: A) total scores of the Dyspnoea-12 questionnaire, B) the score for the quality component of the Dyspnoea-12 questionnaire and C) the emotional response component of the Dyspnoea-12 questionnaire for the participant who did not have re-exacerbations during the study period. Data are mean and standard error. ****Statistically significant difference* **($p < 0.05$) from the final administration (day 98). † No significant difference in the scores across administrations.**

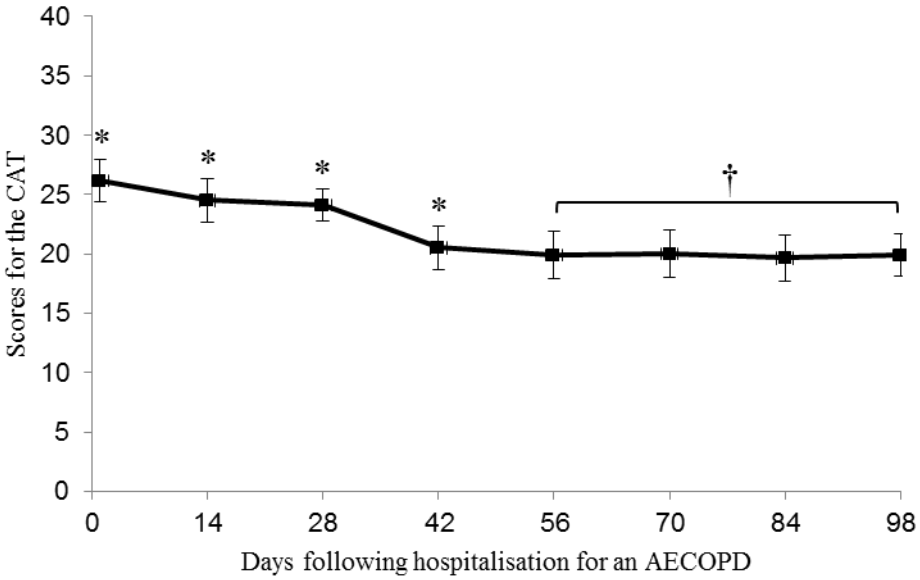

Figure 4-6: Scores of COPD Assessment Test for the participant who did not have re-exacerbations during the study period. Data are mean and standard error. ****Statistically significant difference* **($p < 0.05$) from the final administration (day 98). † No significant difference in the score across administrations on days 56, 70, 84 and 98.**

Table 4-3: Scores obtained for the D-12, the dyspnoea domain of the CRDQ and CAT during periods of an AECOPD and clinical stability for the participant who did not have re-exacerbations

Variable (n = 22)	First administration (AECOPD) *mean ± SD*	Clinical stability *mean ± SD*	Mean change *mean ± SD*	*p value*	Effect size
D-12 total score	25.1 ± 2.6	19.0 ± 1.9	6.1 ± 2.3	*< 0.001**	2.3
Quality component score	14.9 ± 2.3	11.0 ± 1.4	3.9 ± 1.8	*< 0.001**	1.7
Emotional response component score	10.2 ± 1.1	8.0 ± 1.0	2.2 ± 1.3	*< 0.001**	2.0
CRDQ-dyspnoea score (ppi)	2.8 ± 0.4	3.9 ± 0.6	1.1 ± 0.5	*< 0.001**	2.8
CAT score	26.1 ± 1.9	19.4 ± 2.2	6.7 ± 2.8	*< 0.001**	3.5

Abbreviations: AECOPD: acute exacerbation of COPD; CAT: COPD Assessment Test; CRDQ: Chronic Respiratory Disease Questionnaire; D-12: Dyspnoea-12; ppi: points per item; SD: standard deviation. ****Statistically significant difference.*

4.4.5 Scores of the Dyspnoea-12 questionnaire with participants grouped according to Global Initiative for chronic Obstructive Lung Disease grades

4.4.5.1 Data obtained during the first administration in hospital

With all participants included in the analyses, the total D-12 score differed between participants grouped according to their GOLD grades ($p = 0.006$) (Figure 4-7). Differences were demonstrated between GOLD grades 2 and 4 (mean difference = 5.3 ± 1.4, $p = 0.006$) and between GOLD grades 3 and 4 (mean difference = 4.2 ± 3.4, $p = 0.006$). No differences were observed in the score of the quality component of the D-12 between participants grouped according to GOLD grades (Figure 4-7). The score of the emotional response component of the D-12 differed between participants grouped according to their GOLD grades, with differences demonstrated between GOLD grades 2 and 4 (mean difference = 3.0 ± 1.1, $p = 0.002$) and between GOLD grades 3 and 4 (mean difference = 1.8 ± 0.9, $p = 0.019$) (Figure 4-7).

4.4.5.2 Data obtained during the period when participants had returned to clinical stability

With all participants included in the analyses, the total D-12 score differed between participants grouped according to their GOLD grades ($p = 0.006$) (Figure 4-8). Differences were demonstrated between GOLD grades 2 and 4 (mean difference = 4.4 ± 2.0, $p = 0.037$). No differences were observed in the score of the quality component of the D-12 between participants grouped according to GOLD grades. The score of the emotional response component of the D-12 differed between participants grouped according to their GOLD grades, with differences demonstrated between GOLD grades 2 and 4 (mean difference = 2.6 ± 1.8, $p = 0.011$) (Figure 4-8).

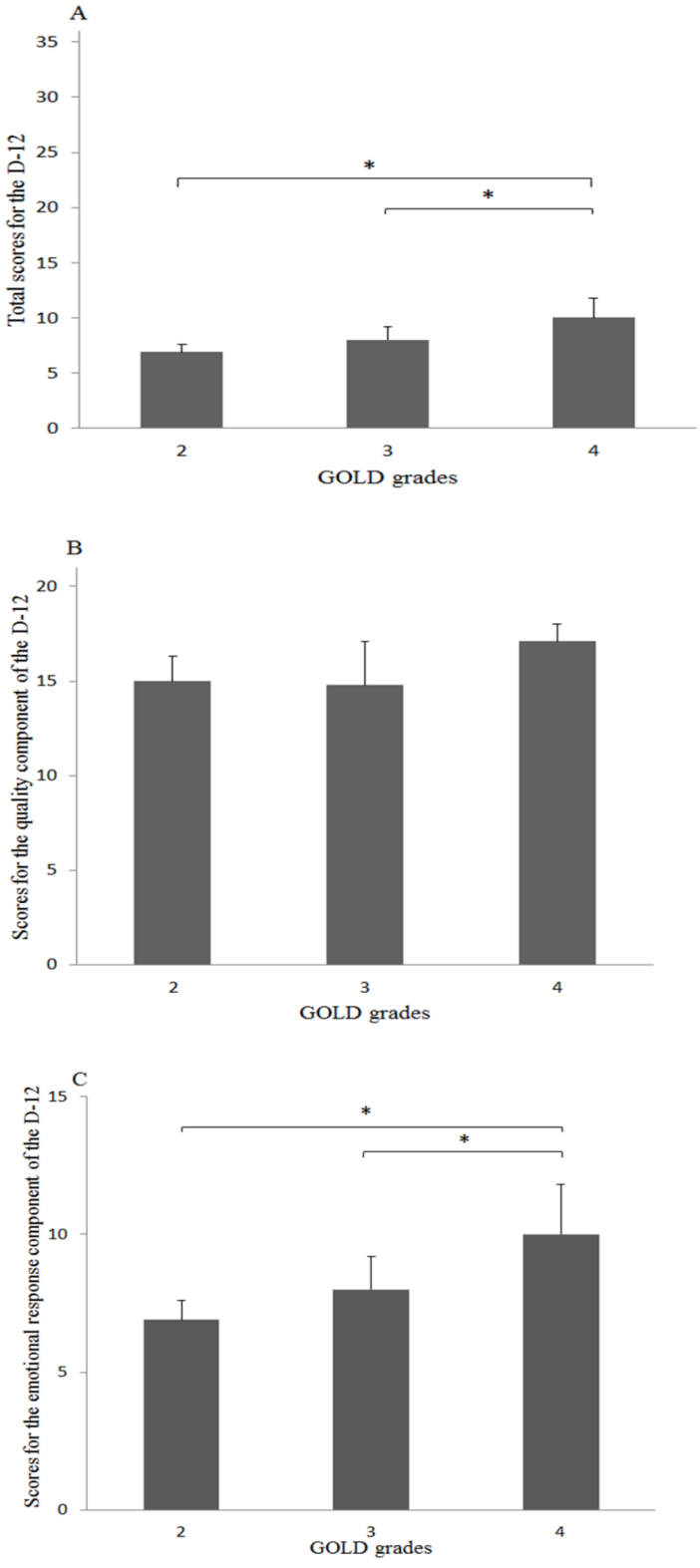

Figure 4-7: A) total score, B) the quality component and C) emotional response component of the Dyspnoea-12 questionnaire with participants grouped according to their disease severity, using grades defined by the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD), at the first administration in hospital. Data are mean scores and standard error. ****Statistically significant difference* **($p < 0.05$).**

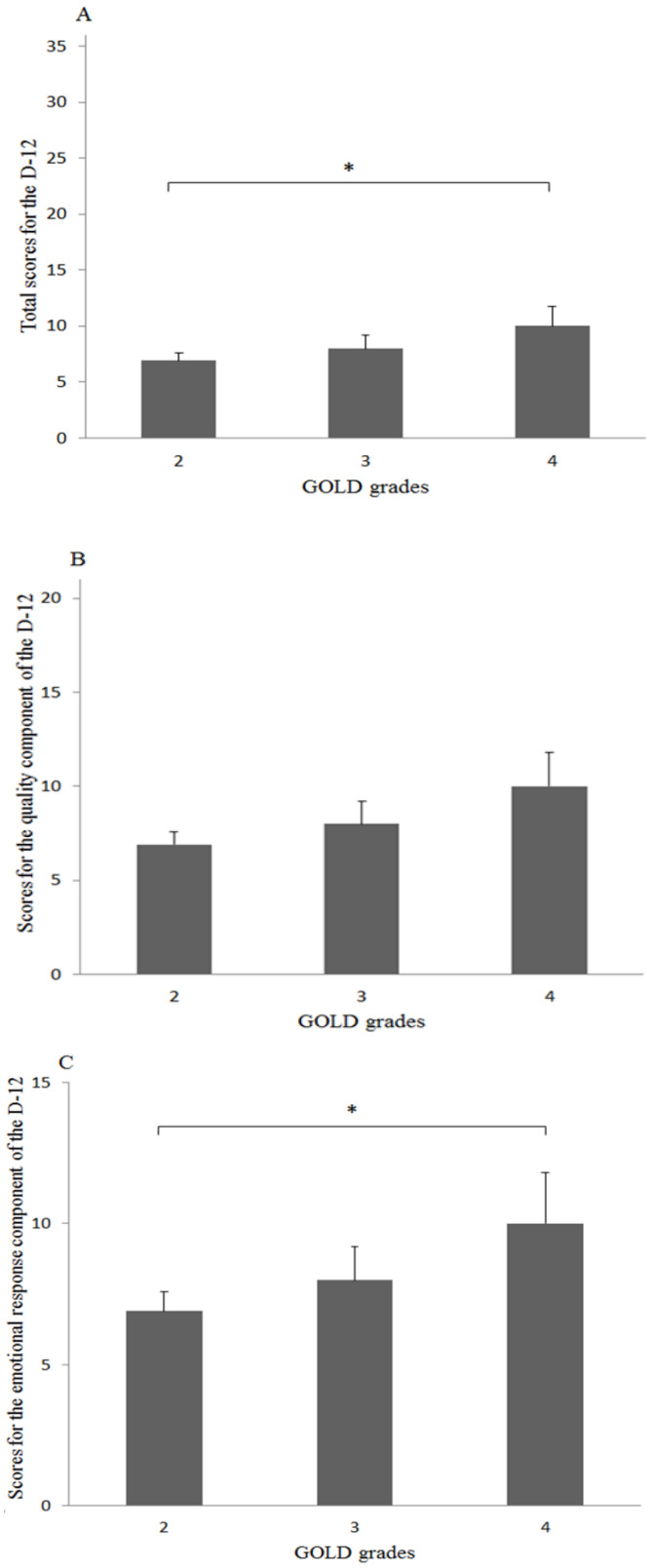

Figure 4-8: A) total score, B) the quality component and C) emotional response component of the Dyspnoea-12 questionnaire with participants grouped according to their disease severity, using grades defined by the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD), when participants had returned to clinical stability. Data are mean scores and standard error. ****Statistically significant difference* **($p < 0.05$).**

4.5 Discussion

This is the first study to determine whether the scores for the total, the quality component and emotional response component of the D-12 differ between periods of an AECOPD and clinical stability for people with COPD. The results of this study have demonstrated that, on average, people with COPD return to clinical stability, defined as no further improvement in dyspnoea during daily life, 70 days following hospitalisation for an AECOPD. The scores for the total, quality and emotional response components of the D-12, as well as the dyspnoea domain of the CRDQ and the CAT, improved significantly between when the participants were hospitalised with an AECOPD and when they had reached a period of clinical stability. The improvement in the quality and emotional response components and total score of D-12 yielded large effect sizes (all ≥ 1.5), according to Cohen's classification (442). The total score of the D-12 and the emotional response component of the D-12 discriminated between people with COPD grouped according to their disease severity, recorded during the first administration of the questionnaires in hospital, and when they had returned to clinical stability.

4.5.1 Time course of recovery following hospitalisation for an AECOPD

The magnitude of the difference in the score of the dyspnoea domain of the CRDQ between the last three consecutive administrations taken during the 98 day follow-up period was below the threshold for clinical importance (< 0.5 ppi) (245). This indicates that, on average, people would not notice any difference in the severity of their dyspnoea during activities of daily living after 70 days from hospitalisation. Therefore, this demonstrates that following hospitalisation with an AECOPD, recovery in terms of no further improvement in dyspnoea during activities of daily living can take up to 70 days.

Previous studies have shown that the trajectory of recovery of symptoms following an AECOPD is quite variable (24, 25). Parker et al (24) demonstrated that 40% of people with a moderate to severe AECOPD had not returned to pre-exacerbation levels of dyspnoea within an average of 41 days following an AECOPD. This suggests that the recovery period may be prolonged in a large proportion of people with COPD. In the present study, a follow-up period of 98 days following

hospitalisation appeared to be appropriate as the majority of people achieved their clinical stability 70 days after hospitalisation for an AECOPD. The long follow-up period used in this study is similar with that reported by Seemungal et al (25) who found that by 91 days following an AECOPD, 91% of people with a moderate to severe AECOPD had returned to their pre-exacerbation levels of respiratory symptoms.

Regarding the time course of recovery, Figure 4.2 shows that the scores for the quality component of the D-12 plateaued two weeks earlier than that observed for the emotional response component of the D-12. This observation indicates that the quality of dyspnoea seems to recover before the emotional response to the sensation of dyspnoea. The measures of the emotional response to dyspnoea recovered over the same administration days as dyspnoea during daily activities, measured using the dyspnoea domain of the CRDQ. These findings suggest that the emotional response to dyspnoea and overall perception of its severity during activities of daily living are associated with each other. This contention is supported by the association previously reported between the emotional response component of the D-12 and the dyspnoea domain of CRDQ ($r = 0.31$, $p < 0.05$) (Chapter 3) (416).

Although the definition of clinical stability used in this study was based on dyspnoea during activities of daily living, this definition appears to be appropriate as the measures of health status plateaued over the same administration days seen when the clinical stability of dyspnoea was achieved. Taken together, these findings can assist clinicians in providing Saudis with an AECOPD and their families' information regarding the expected time course of recovery for dyspnoea and health status following a severe AECOPD.

4.5.2 Changes in the questionnaires between an AECOPD and clinical stability

Significant improvements in the scores, coupled with large effect sizes, were observed for all the questionnaires used in this study between when participants were hospitalised for an AECOPD and when they had reached a period of clinical stability. The large effect sizes were the result of both large mean changes, coupled with the small variability in the magnitude of these differences. The questionnaire most responsive to change during this study was the CAT, which had an effect size

of 3.0. The most likely reason that the CAT was more responsive than the D-12 is that the CAT comprises items relating to a broad range of factors that are likely to be adversely impacted during an AECOPD, such as sleep quality and energy levels, rather than just dyspnoea. The effect size reported in this study is greater than that reported by Jones et al (437) for the CAT following a moderate to severe an AECOPD. Jones et al (437) demonstrated a small effect size (0.19) for the CAT between the first administration (during an AECOPD) and 14 days after an AECOPD. This discrepancy in the effect sizes between the current study and that of Jones et al (437) is likely to have been due to the severity of an AECOPD, as Jones et al (437) did not exclusively include only those with a severe AECOPD.

The magnitude of change seen in the dyspnoea domain of the CRDQ between when people were hospitalised for an AECOPD and when they had returned to clinical stability was 1.0 ± 0.6 ppi. Using Jaeschke et al's (245) definition, in which the clinical improvements in scores of the CRDQ domains were classified as small (≥ 0.5 ppi), moderate (≥ 1.0 ppi) and large (≥ 1.5 ppi), the magnitude of change seen in this study for the dyspnoea domain of the CRDQ following an AECOPD (1.0 ppi) indicates a moderate clinical improvement. The magnitude of change demonstrated in the current study for the dyspnoea domain of the CRDQ is similar to that reported for the dyspnoea domain of the CRDQ (0.79 ppi) on completion of a program of pulmonary rehabilitation (45). Further, it is also similar to that reported by Aaron et al (53) who explored changes in the dyspnoea domain of the CRDQ following an AECOPD. Aaron et al (53) demonstrated a magnitude of change of 1.3 ± 0.2 ppi between the first administration of the dyspnoea domain of the CRDQ (during an AECOPD) and 10 days following an AECOPD. Thus, the effect size of 2.5 for the dyspnoea domain of the CRDQ reported in the present study is greater than that calculated by Aaron et al (53), who reported an effect size of 1.3. A possible explanation for this discrepancy is, in the present study, there was smaller variability in the scores reported at the first administration (SD at baseline = 0.4 ppi) compared to that obtained by Aaron et al at the first administration (SD at baseline = 1.0 ppi) (53). The magnitude of change in the dyspnoea domain of the CRDQ seen in the current study seems to be less than what has been reported in a previous study (24). Parker et al (24) assessed dyspnoea, using the individualised dyspnoea domain of the CRDQ, in 22 people with moderate to severe AECOPD. The authors demonstrated a

magnitude of change in the dyspnoea domain of the CRDQ between the first administration (during AECOPD) and the final administration (60 days following an AECOPD) of 1.6 ± 0.4 ppi. However, a people in the current study had a severe AECOPD, whereas in the study by Parker et al (24), only seven out of 20 people had a severe AECOPD. Therefore, the discrepancy in the magnitude of change in dyspnoea between the present study and that of Parker et al (24) may reflect the differences in the severity of an AECOPD as well as differences in the versions of the CRDQ that were used (i.e. standardised dyspnoea domain vs individualised dyspnoea domain).

Regarding the changes seen in the D-12, similar effect sizes were obtained for the quality and emotional response components of the D-12 (effect sizes 1.6 and 1.7, respectively), which shows that both components of the D-12 have a similar capacity to change following a severe AECOPD. Further work is needed to determine the threshold for the minimal clinical important difference of the D-12. Using the D-12 for assessing dyspnoea recovery following an AECOPD will provide health professionals information related to the severity of both the quality of dyspnoea sensation and emotional response to dyspnoea. In addition, the D-12 could be used to provide people who have been hospitalised with a severe AECOPD, and their families, information regarding the time course recovery of dyspnoea.

Given that the effect sizes for the total score for the D-12 was a similar to the effect size for the dyspnoea domain of the CRDQ (effect size 2.1 vs 2.5), it is possible that the total score for the D-12 will demonstrate similar responsiveness to the CRDQ following interventions that aim to ameliorate dyspnoea, such as bronchodilators and pulmonary rehabilitation.

4.5.3 The impact of an AECOPD on dyspnoea, HRQoL and health status

Although the proportion of females in the present study is very small, it appears that females and males experience the same quality of dyspnoea sensation and emotional response to dyspnoea at an AECOPD period. In addition, during the period of an AECOPD, both genders seem to experience the same perception of dyspnoea during their activities of daily living and poor health status.

This is the first study to assess dyspnoea in both components during the period of a severe AECOPD. The findings of this study demonstrated that people with COPD appeared to experience worse dyspnoea in both the quality and the emotional response to dyspnoea sensation when compared to their severity of dyspnoea reported during the period of clinical stability. This finding, overall, is similar to that reported in different studies that showed people with COPD had worse dyspnoea during an AECOPD, dyspnoea was measured using different tools such as the modified Medical Research Council and Borg scale (440, 443, 444). The results of this study highlight the importance of targeting an intervention that aims to reduce the severity of both components of dyspnoea during an AECOPD.

During an AECOPD, people in the present study reported worse dyspnoea related to daily activity and poor health status compared to that reported during the period of clinical stability. These findings of this study are the first to report dyspnoea related to daily activities, using the dyspnoea domain of the CRDQ, and health status, using the CAT, during an AECOPD in the Gulf countries, especially in Saudi Arabia. Parker et al (24) assessed dyspnoea, using the individualised dyspnoea domain of the CRDQ, in 20 people with COPD from Canada during an AECOPD. The authors reported a similar score (2.4 ± 0.3 ppi) for the dyspnoea domain of the CRDQ to that obtained in the present study (2.7 ± 0.4 ppi). This indicates that, during an AECOPD, people with COPD from Saudi Arabia and Canada experience similar severity of dyspnoea during their daily activities. Due to different tools that are available to measure HRQoL in people with COPD it was not possible to compare dyspnoea related daily activities during an AECODP in Saudi population with other international findings.

Poor health status was observed in Saudi people with COPD during an AECOPD. The score of the CAT (26.2 ± 2.0) reported in this study is similar to the CAT scores reported in 224 people with COPD from Spain (22.2 ± 8.4) (440) and in 75 people with COPD from United Kingdom (24.1 ± 7.3) during severe AECOPDs (445). These findings demonstrate that severe AECOPDs lead to poor health status as observed in those populations.

4.5.4 The impact of a re-exacerbation

When the analyses were limited to the participants who did not have re-exacerbations (i.e. those who did not experience a second exacerbation during the recovery period), the results were similar to those presented in the main analyses, in terms of the time period required to reach clinical stability. This similarity is because the majority of the participants (76%) in this study did not have-re-exacerbations. However, the effect sizes for the questionnaires for the participants who did not have re-exacerbations appeared to be greater than those obtained for the main analyses which included all participants. Although both components of the D-12 demonstrated large effect sizes in the participants who did not have re-exacerbations, the emotional response component seemed to change more than the quality component (effect size of 2.0 *versus* 1.6).

4.5.5 Capacity of the Dyspnoea-12 questionnaire to discriminate between people grouped according to disease severity

The current study demonstrated that during hospitalisation with an AECOPD, people with very severe COPD experienced greater emotional response to dyspnoea compared to those with moderate or severe COPD. Compared to people with moderate COPD, the greater severity of emotional response to dyspnoea in people with very severe COPD was still evident even when the people had returned to clinical stability. The difference in the mean scores of the D-12 between people with moderate and those with very severe COPD when they had returned to clinical stability is concordance with that observed between those with stable moderate and very severe COPD (Chapter 3) (416). This suggests that interventions which target the emotional response to dyspnoea, such as cognitive behavioural therapy, may be of more value in those with more severe disease. The lack of differences between people grouped according to their disease severity in the quality of dyspnoea during periods of an AECPD and clinical stability indicates that people with different disease severity have a similar quality of dyspnoea sensation during both an AECOPD and periods of clinical stability.

4.6 Limitations

This study had some limitations. The small sample size with the small proportion of females in this study can be a limitation. However, the present study had an adequate power and recruited the minimum number of participants to demonstrate the sensitivity of the D-12 to change following an AECOPD. In addition, the proportion of females to males in the sample (4 out of 29 participants; 13.8%) is lower than the proportion of females (1.0%) to males (3.5%) with COPD in the population in Saudi Arabia (22.2%) (432). This may limit the generalisability of the results especially in females. A large study, including females, from different regions in Saudi Arabia is required to increase the generalisability of the Arabic version of the D-12. Furthermore, illiteracy in the older adult Saudi population should also be considered. This was the main reason for those who did not meet the study criteria. Therefore, developing an interviewer-administered version of the D-12 is recommended. The results of this study are restricted to those who experienced a severe AECOPD that required hospitalisation. Therefore, the results may not be generalisable to changes seen following a mild or moderate AECOPD. Changes in the scores of D-12 were not tested by administering a given intervention that is known to change dyspnoea. Instead, this study investigated changes in the D-12 scores in response to clinical status. Therefore, further research is required to investigate the ability of the D-12 detect changes in response to therapeutic interventions, such as pulmonary rehabilitation. Finally, the capacity to detect changes in the D-12 between participants grouped according to their disease severity is likely to have been comprised by the limited number of people in GOLD grades 2 and 4.

4.7 Conclusions

This study has demonstrated that overall, following hospitalisation with an AECOPD, recovery, in terms of no further improvement in dyspnoea during activities of daily living, can take up to 70 days. Scores from all questionnaires improved significantly between when people were hospitalised with an AECOPD and when they had reached a period of clinical stability. The effect size of the D-12 was similar to that obtained for the dyspnoea domain of the CRDQ. In addition, the D-12 was able to discriminate between people grouped according to disease severity.

Therefore, it appears that the D-12 is suitable to use in the clinical setting for evaluating changes in dyspnoea.

CHAPTER 5

PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOUR OF SAUDI MALES WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A COMPARISON WITH AGE AND GENDER MATCHED HEALTHY CONTROLS

5.1 Overview

In both healthy and diseased populations, health benefits of regular participation in ≥ 30 minutes of moderate intensity physical activity (activities that require and energy expenditure ≥ 3 metabolic equivalent units [METs]), on at least five days each week, are well documented (54). Walking is a common form of physical activity that is generally safe, convenient and inexpensive (369). In adults, work has shown that walking at a cadence ≥ 100 steps/min appears to be equivalent to moderate intensity physical activity (62, 64-66). Compared with healthy controls, people with chronic obstructive pulmonary disease (COPD) spend less time of their waking hours participating in physical activity (i.e. walking) and more time in sedentary behaviour (i.e. sitting) (56, 57). This higher proportion of time spent in sedentary behaviour can have deleterious health outcomes including the risk of developing diabetes, cardiovascular disease and premature mortality (401). Although people with COPD have lower levels of physical activity when compared with healthy controls, these low levels have been shown to vary between people from different countries (81). Therefore, data obtained in one country may not be representative of the time spent in physical activity and sedentary behaviour of people from other countries, due to factors such as different ethnicity, culture, geographical location, environment and socioeconomic factors (81, 446).

Data on physical activity from different countries in the world have shown that males are more active than females (447-451). Similar findings have been reported that, compared to males, females in the Gulf region are more inactive (74, 452-454). The reasons for the low levels of physical activity and sedentary behaviour among Saudi females compared with both Saudi males and females from different countries are

poorly explored. There are certain sociocultural factors in the Gulf region that seem to be barriers to females' physical activity such as wearing an abaya (a long dress) outside the house, limited freedom of movement outside of the house, depending on a driver, and employing domestic helpers (455, 456). In addition, the hot climate is an important barrier for both males and females for exercising outdoors. Males also experience significant barriers such as employing domestic helpers, and regular use of automobiles. However, compared to females, males have more freedom of movement outside of the home.

In people with COPD, dyspnoea, or the sensation of breathing discomfort that occurs during exertion, is generally believed to be the main limitation to participating in physical activity (10, 56). This belief is supported by the associations demonstrated between dyspnoea and physical activity (57, 82, 84). Information on physical activity and sedentary behaviour in people with COPD from Saudi Arabia has not been reported to date. In addition, it is unknown whether the quality of dyspnoea or the emotional response to dyspnoea has the greatest negative impact on participating in physical activity and accumulating time in sedentary behaviour in people with COPD.

Data presented in this chapter are only for males. It was not possible to recruit females to this study. In Saudi culture, it is not acceptable for a man to talk to women in public areas unless they are a family. Therefore, the male primary investigator (M.A) could not recruit female participants and as he did not have a female colleague available to assist with the study it was not possible to include females in the study.

5.1.1 Overall aim

The primary aim of this study was to compare physical activity and sedentary behaviour of Saudi males with COPD with that of healthy age and gender-matched controls.

The secondary aim was to investigate the associations between the quality and emotional response components of the Dyspnoea-12 questionnaire (D-12) with the time spent in walking based activity and sedentary behaviour in males with COPD.

5.1.2 Research hypotheses

The primary hypothesis for this study was that physical activity and sedentary behaviour will differ between males with COPD and healthy controls.

The specific hypotheses are;

i. Males with COPD will spend less time in walking based activity and more time in sedentary behaviour during waking hours compared with healthy controls.
ii. The way in which time spent in walking based activity and sedentary behaviour were accumulated will differ during waking hours between males with COPD and healthy controls.
iii. Males with COPD will have lower peak and average 30-minute peak cadence compared to healthy controls.
iv. Males with COPD will have a smaller percentage of males who participated in sufficient physical activity when compared to healthy controls.

The secondary hypothesis for study was that the quality and emotional response components of the D-12 will be associated with the time spent in walking based activity and sedentary behaviour in males with COPD.

5.2 Methodology

5.2.1 Study design

This study was cross-sectional in design. Data collection was undertaken between February 2013 and March 2014. Approval to conduct the study was granted by the Institutional Review Board at King Fahad Medical City, Saudi Arabia (approval number 12/312) and the Human Research Ethics Committee of Curtin University, Australia (approval number HR 24/2013).

5.2.2 Participants

Two groups were recruited. These were males with COPD and healthy controls.

5.2.2.1 Males with COPD

5.2.2.1.1 Recruitment

Males with COPD were recruited from the outpatient pulmonary clinics at King Fahad Medical City in Riyadh, Saudi Arabia. During the clinic visit, consecutive males with COPD were asked by their respiratory physician whether they were interested in being told about the study. Those who expressed an interest were contacted by the primary investigator (MA) who provided all necessary information related to the study. Written, informed consent was obtained from the participants prior to data collection.

5.2.2.1.2 Inclusion criteria

The inclusion criteria were; (i) males, (ii) a diagnosis of COPD defined as post-bronchodilator forced expiratory volume in one second (FEV_1)/ forced vital capacity (FVC) < 0.7 and post-bronchodilator FEV_1< 80% predicted (10), (iii) a stable condition for at least two months and (iv) aged ≥ 40 years. Further, only those who were retired (i.e. no longer undertaking paid employment) were included. This decision was made in order to minimise any confounding influence the nature of someone's work may have had on their participation in daily physical activity and sedentary behaviour.

5.2.2.1.3 Exclusion criteria

Exclusion criteria comprised; (i) presence of any comorbid condition thought to adversely affect the capacity to participate in physical activity, such as uncontrolled cardiovascular disease or severe musculoskeletal condition, (ii) use of supplemental oxygen, (iii) use of a gait aid and, (iv) inability to read and write the Arabic language.

5.2.3 Healthy controls

5.2.3.1 Recruitment

A sample of convenience of healthy males was recruited through the distribution of flyers. The first sources were mosques and the relatives of people with COPD. Two

mosques in Riyadh were approached every two months. The capacity of these mosques was approximately 2,500 persons each. Flyers were distributed to males attending these mosques. The second source was family members of participants with COPD. Participants with COPD were asked if they had family members who would like to participate in the study. Written, informed consent was obtained from the participants prior to data collection.

5.2.3.1.1 Inclusion criteria

Inclusion criteria were; (i) males who were free from a serious health condition, (ii) normal spirometry and, (iii) retired. In order to optimise the likelihood that the COPD and healthy controls were balanced in terms of age, males with COPD were recruited first and their mean age and standard deviation (SD) were determined. Thereafter, healthy people were recruited if they were aged within ±1 SD of the mean age of the COPD group.

5.2.3.1.2 Exclusion criteria

Exclusion criteria comprised; (i) smoking history of ≥ 10 years, (ii) presence of any co-morbid condition thought to adversely affect the capacity to participate in physical activity such as uncontrolled cardiovascular disease or severe musculoskeletal condition, determined by an interview and screening of current medications, (iii) use of a gait aid and, (iv) inability to read and write the Arabic language.

5.2.4 Protocol

Participants with COPD were required to attend, at King Fahad Medical City, one session of two-hours duration. During this session, measures were obtained of post-bronchodilator FEV_1, FVC, dyspnoea using the D-12 and six-minute walk distance (6MWD). Also, participants' characteristics such as age, height and weight were recorded. At the completion of this session, each participant was fitted with a Stepwatch Activity Monitor (Stepwatch, Cyma Corporation, Seattle, WA, USA; [SAM]). Participants were required to wear the SAM during waking hours for eight consecutive days. They were instructed to remove the monitor while showering and during swimming activities as well as sleeping overnight. Participants were requested

to maintain their usual daily physical activity while wearing the SAM. All participants were given a reply-paid registered-post envelope in which to return the SAM after completion of their participation in the study.

The protocol for the healthy control group was similar to that used for the COPD group. However, participants in this group were not required to complete the D-12 or perform the six-minute walk test.

5.2.5 Measurements

5.2.5.1 Physical activity

Physical activity was measured using the SAM, which is a microprocessor-linked sensor enclosed within a lightweight (38 g), pager-sized, durable casing, which responds to time, acceleration and position. It has been shown to have an excellent capacity to accurately detect steps in healthy elderly people, as well as males with COPD regardless of walking speed or the use of walking aids (e.g. wheeled-walker) (377, 457, 458). The SAM was attached to the participant's right ankle using a Velcro strap. This device has a sampling frequency of 128 Hz and data were available in one-minute epochs. The data correspond to the number of steps taken by the right leg and therefore the step count was doubled to provide the total number of daily steps. The SAM was initialised for each participant prior to data collection. During this initialisation procedure, the height of each participant was entered into the SAM software, and the settings related to 'range of walking speed' and 'leg motion' were selected as 'moderate' and 'normal' respectively. For each participant, the first 40 steps taken while wearing the SAM were observed to ensure that the device was detecting steps correctly, as indicated by a flashing light emitting diode upon heel strike (459).

Wearing the SAM over eight consecutive days was considered unlikely to affect participants' daily routines as the monitor was small, light and provided no feedback (460).

5.2.5.2 Dyspnoea

Dyspnoea was measured using the Arabic D-12, which comprises 12 items that assess dyspnoea severity. Each item is graded in terms of its severity using a four-point scale ranging from none (score = 0) to severe (score = 3) (23). The D-12 produces a total score from 0 to 36, with higher scores indicating greater severity of dyspnoea. Of the 12 items seven relate to the quality of dyspnoea, with scores ranging from 0 to 21, and five related to the emotional response to dyspnoea, with scores ranging from 0 to 15. The D-12 has been shown to be reliable and valid in Saudi nationals with COPD (Chapter 3) (416).

5.2.5.3 Lung function

Post-bronchodilator FEV_1 and FVC were measured using an Easy One Spirometer (NDD Medical Technologies, Massachusetts, USA), according to the guidelines of the American Thoracic Society (422). The spirometer device was calibrated in accordance with the manufacturer's recommendations. Measures were expressed as a percentage of the predicted values previously established in a local population (423).

5.2.5.4 Functional exercise capacity

Functional exercise capacity for participants with COPD was evaluated using the 6MWD, which was undertaken according to a protocol based on recommendations made by the European Respiratory and American Thoracic Societies (307). The 6MWD was performed over a 45-meter level straight course within an enclosed corridor. Standardised instructions were read to each participant prior to the commencement of the test, and standardised encouragement was given at the end of every minute. To account for improvements resulting from familiarisation (424), two tests, separated by a 30-minute rest period, were conducted and the best distance achieved was recorded as the test result. The 6MWD was expressed in absolute values and as a percentage of the predicted values previously established in an international sample (425).

5.3 Statistical analyses

5.3.1 Sample size calculations

A previous European study that measured walking time in people with COPD and healthy controls reported that those with COPD participated in walking for (mean ± SD) 44 ± 26 minutes/day and healthy controls participated in walking for 81 ± 26 minutes/day (56). Using these data, it appears that people with COPD were, on average, 46% less active than their retired healthy age and gender-matched counterparts (56). For the current study, a more modest difference (i.e. a 25% reduction in physical activity) was expected between Saudi nationals with COPD and their healthy controls. This was because it was expected that the general population of Saudis would be less active than those living in Western countries (74). Specifically, the weather in Saudi Arabia tends to be very hot in the summer and cold in the winter which limits the capacity to participate in outdoor physical activity. Data from an earlier study that measured the level of physical activity in Saudi nationals using the International Physical Activity Questionnaire revealed that they generally participate in little physical activity (72). As a European study demonstrated that healthy people walked for 81 ± 26 minutes each day, a 25% reduction is equivalent to 20 minutes (25% of 81 minutes = 20 minutes). Assuming the same SD as reported in the European study, it was calculated that to detect of difference in walking time of 20 ± 26 min/day between the COPD and healthy control groups ($\alpha = 0.05$, $1-\beta = 0.8$), a sample size of 28 was needed for each group.

5.3.2 Data management

Data recorded by the SAM were exported to Microsoft Excel™ (version 2010, Microsoft, Redmond, USA). Data collected on the day that the SAM was first fitted were discarded from analyses as data for this day were incomplete. Overnight sleep time, which would have been included in the output and recorded as 0 steps/min, was also discarded from analyses. This was because sleep is not considered as sedentary behaviour (350), and also to optimise the accuracy of the time spent in sedentary behaviour. Therefore, waking hours were defined in accordance with earlier work that used the same monitor to measure physical activity in people with knee osteoarthritis (461). That is, waking hours were defined as the period between when

the first step was registered in the morning to when the last step was registered in the evening.

5.3.2.1 Defining minimal acceptable wear time for the stepwatch activity monitor data required to be included in the analyses

5.3.2.1.1 Number of measurement days

The minimum number of acceptable days of wearing a physical activity monitor varies between studies (see discussion). Consistent with earlier work a minimum of five days of wear time was required to include the data in this study's analyses (85).

5.3.2.1.2 Number of measurement hours per day

The minimum wear time for a physical activity monitor in terms of number of hours per day varies between studies. Consistent with earlier work done in elderly people, a pragmatic option of a minimum of 10 hours a day was used to define the minimum acceptable wear time needed to be included in analyses (388).

5.3.2.1.3 Weekdays versus weekends

Outcomes of monitoring physical activity in people with moderate to very severe COPD was found to not differ between weekdays and weekends (78). Therefore, this study chose to include a minimum of five days of wear time, regardless of weekdays or weekends.

5.3.2.2 Exploring the time spent in walking based activity and sedentary behaviour

Walking based activity was defined as ≥ 1 step/min and sedentary behaviour was defined as 0 steps/min. Time spent in walking based activity and sedentary behaviour was expressed as absolute minutes and also as a percentage of total wear time (i.e. to account for differences in wear time between participants). Total daily steps count were calculated for both groups.

5.3.2.3 Exploring the time spent in walking based activity undertaken at difference cadences

Wear time was divided into cadence categories, using the same thresholds described in the National Health and Nutrition Examination Survey (NHANES) (67). Specifically, walking cadences were categorised into the following domains: 1 to19 steps/min (i.e. incidental movement), 20 to 39 steps/min (i.e. sporadic movement), 40 to 59 steps/min (i.e. purposeful steps), 60 to 79 steps/min (i.e. slow walking), 80 to 99 steps/min (i.e. medium walking), 100 to 119 steps/min (i.e. brisk walking), and ≥ 120 steps/min (i.e. fast locomotor movements) (67). Time in each of these cadence bands was expressed as absolute minutes and also as a percentage of total wear time (i.e. to account for differences in wear time between participants).

5.3.2.4 Exploring patterns of accumulation for both walking based activity and sedentary behaviour

To explore the way in which time was accumulated for both walking based activity and sedentary behaviour, the duration of each bout of time spent in walking based activity (defined as any one-minute period during which ≥ 1 step/min was recorded) and sedentary behaviour (defined as any one-minute period during which 0 steps/min were recorded) was determined. This was achieved using a three-step process. First, SAM data were scanned for walking based activity. Second, the duration of each bout of walking based activity that occurred during waking hours was derived by summing the number of consecutive cells in which ≥ 1 step/min were recorded. That is, for the pattern of one-minute epochs of SAM data outlined below, a bout duration for walking based activity was recorded as one minute as only one of the one-minute epochs had ≥ 1 step/min recorded.

0, 0, 0, 0, 0, 0, 24, 0, 0, 0

Similarly, for the pattern of one-minute epochs of SAM data outlined below, a bout duration for walking based activity was recorded as five minutes as five of the one-minute epochs had ≥ 1 step/min recorded.

0, 0, 0, 0, 30, 10, 24, 28, 50, 0

Third, for each measurement day included in analyses, the duration of all bouts of walking based activity were averaged.

This process was then repeated for sedentary behaviour. That is, SAM data were scanned for sedentary behaviour. Second, the duration of each bout of sedentary behaviour that occurred during waking hours was derived by summing the number of consecutive cells in which 0 steps were recorded. That is, for the pattern of one-minute epochs of SAM data outlined below, a bout duration for sedentary behaviour was recorded as one minute.

10, 24, 28, 50, 50, 24, 0, 10, 24, 28

Similarly, for the pattern of one-minute epochs of SAM data outlined below, a bout duration for sedentary behaviour was recorded as five minutes.

10, 24, 0, 0, 0, 0, 0, 10, 24, 28

Third, for each measurement day included in analyses, the duration of all bouts of walking based activity were averaged.

5.3.2.5 Exploring peak and 30-minute peak cadences for walking based activity

Stepwatch Activity Monitor data were sorted in descending order of cadence. Thereafter, the peak (the one-minute epoch during which the highest cadence was recorded) and average 30-minute peak cadence (the average of the 30 individual one-minute epochs, during which the highest cadences were recorded, not necessarily consecutive) were obtained for each day. The method used in this study for analysis of the peak intensity of walking abased activity is the same method reported by NHANES (462).

5.3.2.6 Exploring the proportion of participants who met the criteria for participating in sufficient walking based activity

There is controversy in the literature regarding the number of steps that are required to meet the current recommendations for participation in physical activity that will produce health benefits (54). Tudor-Locke et al (355) reviewed the results of studies that used an accelerometer to translate the current physical activity recommendations

into daily steps in older adults. These authors concluded that accumulating 7,000 to 10,000 steps/day is equivalent to performing 30 minutes per day of moderate to vigorous intensity physical activity. These findings are similar to those reported in the guidelines of the American College of Sports and Medicine (ACSM) who recommend that adults should accumulate at least 7,000 steps daily (54). Based on these data, participants in this study who had SAM data for seven days and accumulated at least 7,000 steps/day in five days or more, were deemed to have met the criteria for participating in sufficient walking based activity.

5.3.3 Statistical analyses

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS version 21.0, Armonk, NY: IBM Corp, USA). The distribution of data was examined by graphical (frequency histograms and box plots) and statistical methods (Shapiro-Wilk test). Data that did not follow a normal distribution were analysed using non-parametric statistical tests. Prior to undertaking the comparisons of data between the participants with COPD and healthy controls, for each group, differences in walking based activity and sedentary behaviour variables were compared across the days that SAM data were available. These within-group analyses were needed to show that there were minimal differences between days and therefore, that data could be averaged across days for the purpose of the between-group comparisons. Within-group comparisons of walking based activity and sedentary behaviour variables were performed using a one-way repeated measures analysis of variance (ANOVA) or Friedman's ANOVA for parametric or non-parametric data respectively.

In the absence of any large differences between days within groups, all walking based activity and sedentary behaviour variables were averaged across the days that the SAM data were available. Thereafter, data were compared between the participants with COPD and healthy controls using either independent-samples *t*-tests or Mann-Whitney U tests for parametric or non-parametric data, respectively. The Chi-squared statistic was used to compare the proportion of participants who accumulated $\geq$ 7,000 steps/day.

Associations between the quality and emotional response components of the D-12 and time spent (expressed as percentage of total wear time and minutes) in walking based activity and sedentary behaviour in participants with COPD were examined using Pearson or Spearman's correlations for parametric or non-parametric data, respectively. For all analyses, a p value ≤ 0.05 was considered significant. Data are expressed as mean ± SD unless otherwise stated.

5.4 Results

5.4.1 Participants

Seventy-two males with COPD were screened for possible inclusion into the study. Twenty males (28%) were not eligible to participate in the study, of whom ten (50%) were not clinically stable for the last two months. Seven (35%) of the 20 males who did not meet the study criteria were not retired. The remaining three (15%) of the 20 males were on supplemental oxygen and, therefore, were not eligible for participation in the study.

Fifty-two (72%) were eligible and approached to participate. Of these 52 males, a total of 34 consented to participate (consent rate of 65%). The reasons for not participating are outlined in Figure 5-1. Four of the 34 (12%) were not included in the analyses pertaining to walking based activity and sedentary behaviour because of hospitalised with an acute exacerbation of COPD during the monitoring period (n = 1), insufficient wear time ≤ 10 hour/day (n = 1) or were SAM data were not unable to be retrieved as they did not return the device (n = 2) (Figure 5-1).

Of the 30 participants in the COPD group who had their walking based activity and sedentary behaviour data analysed, 21 (70%) wore the SAM for ≥ 12 hours/day on all seven days, nine (30%) wore the monitor for ≥ 12 hours/day for six days and one (3%) wore the monitor for ≥ 12 hours/day for five days. Their characteristics are presented in Table 5-1.

Forty healthy controls were screened for possible inclusion into the study. Eight males (20%) did not meet the criteria of the study. Five males (62%) of the eight were not retired and the other three (38%) had abnormal spirometry data.

Thirty-two (80%) were eligible and approached to participate. These 32 males consented to participate (consent rate of 100%) in this study. Three of the 32 (9%) were excluded from the analyses pertaining to walking based activity and sedentary behaviour because they did not return the activity monitors.

Of the 29 healthy controls who had their walking based activity and sedentary behaviour data analysed, 26 (90%) wore the SAM for ≥ 12 hours/day for all seven days, and three (10%) wore the monitor for ≥ 12 hours/day for six days (Figure 5-1). Their characteristics are presented in Table 5-1.

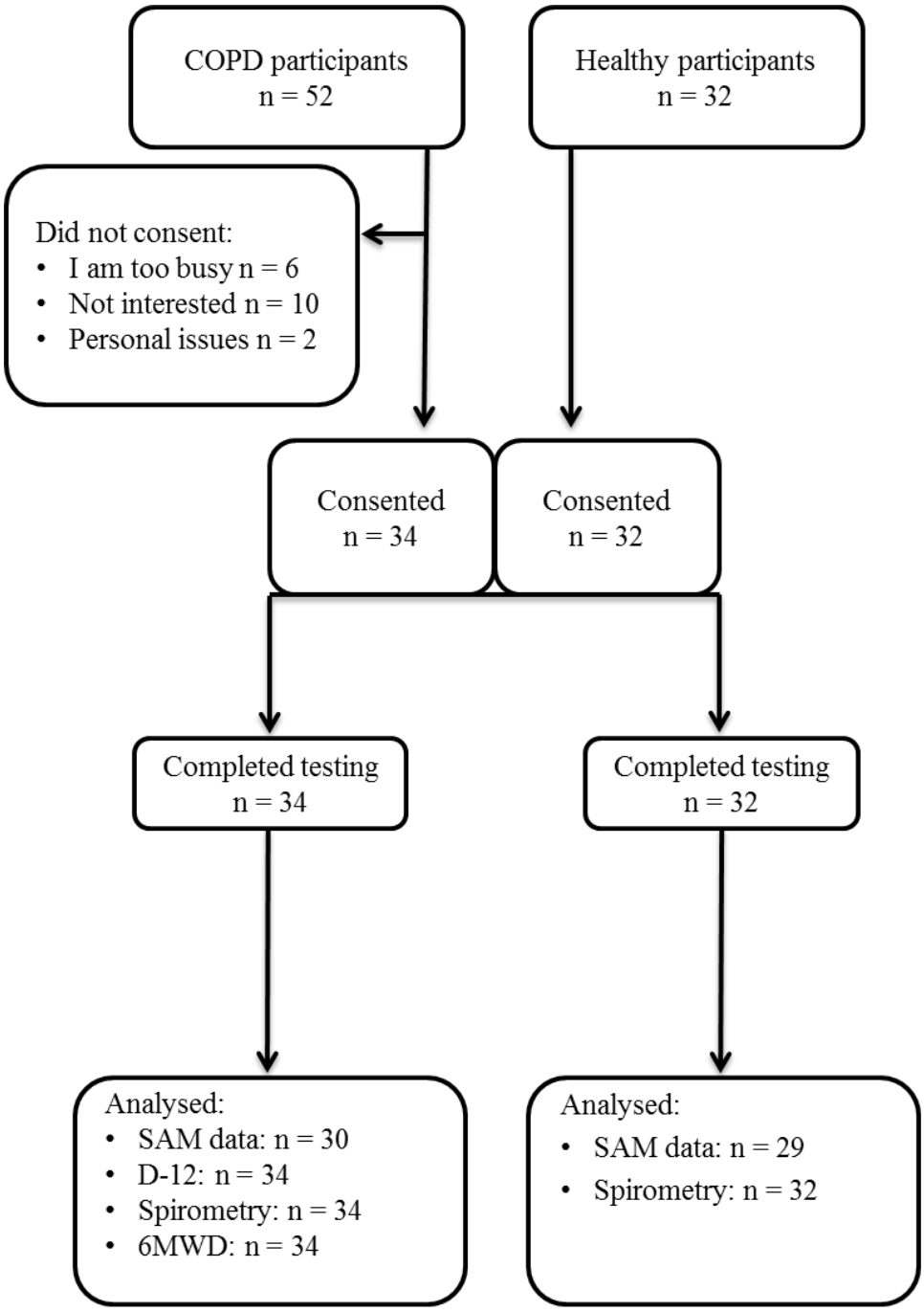

Figure 5-1: Study flow diagram

Abbreviations: Abbreviations: D-12, Dyspnoea-12 questionnaire; SAM, StepWatch^{TM} Activity Monitor; 6MWD, six-minute walk distance.

Table 5-1: Characteristics of participants

Variable	COPD participants (n = 34) *mean ± SD*		Healthy controls (n = 32) *mean ± SD*		*p value*
Age, years	61.9 ± 5.2		63.1 ± 3.6		*0.339*
BMI, kg/m^{-2}	27.9 ± 4.4		28.4 ± 3.8		*0.655*
Smoking, pack/years	48.3 ± 18.3		0.9 ± 3.1		*< 0.001**
FEV_1, L	1.41 ± 0.55		2.60 ± 0.31		*< 0.001**
FEV_1, % predicted	46 ± 16		91 ± 5		*< 0.001**
FVC, L	2.51 ± 0.64		3.09 ± 0.36		*< 0.001**
FVC, % predicted	67 ± 14		88 ± 6		*< 0.001**
FEV_1/FVC, %	55 ± 12		84 ± 6		*< 0.001**
D-12 total score	19.1 ± 3.5				
Quality component score	10.9 ± 2.4				
Emotional response component score	8.2 ± 1.6				
6MWD, m	347 ± 75				
6MWD, % predicted	63 ± 12				
	n	%	**n**	%	
Smoking status					
Current smoker	18	53	4	13	*< 0.001**
Ex-smoker	16	47	2	6	*< 0.001**
Never smoked	0	0	26	81	*< 0.001**
Comorbidities					
Hypertension	20	59	19	59	0.673
Diabetes mellitus	16	47	13	41	*0.235*
Stable heart disease	7	21	4	13	*0.347*
GORD	23	68	16	50	*0.239*
Dyslipidaemia	17	50	10	31	*0.153*
Others	18	53	7	22	*< 0.001**
GOLD grades					
2	13	38			
3	11	32			
4	10	30			

Data are expressed as mean ± SD: standard deviation or number (%). BMI: body mass index; D-12: Dyspnoea-12; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease (2: moderate, 3: severe and 4: very severe), GORD: gastro-oesophageal reflux disease and 6MWD: six-minute walk distance. * *Significant difference between groups.*

5.4.2 Number of measurement days and number of measurement hours per day

There were no differences between the COPD and healthy participants in the number of days of SAM data included in the analyses (6.8 ± 0.5 days *versus* 6.9 ± 0.3 days; $p = 0.36$), or in the average daily wear time (13.4 ± 0.8 hours/day *versus* 13.5 ± 0.5 hours/day; $p = 0.40$).

5.4.3 Within group comparisons of walking based activity and sedentary behaviour variables

5.4.3.1 COPD participants

There were no differences between days in the time spent in walking based activity and sedentary behaviour expressed as minutes (Table 5-2) or in the percentage of total wear time (Figure 5-2). No differences were observed between total daily step counts between days (Table 5-2). Figure 5-3 and Figure 5-4 illustrate the percentage of waking hours spent in walking based activity when divided into cadence bands. When walking based activity was divided into cadence bands and expressed in minutes, there was no difference between days ($p > 0.05$) (Table 5-2). When walking based activity was divided into cadence bands and expressed as a percentage of total wear time, there was a significant difference in the percentage of waking hours accumulated at a cadence between 1 and 19 steps/min ($p = 0.047$) (Figure 5-3). Post-hoc analyses revealed that the percentage of waking hours accumulated at a cadence between 1 and 19 steps/min on Sunday (11.0 ± 4.7) was lower than that measured on Wednesday (15 ± 6.3, $p = 0.011$) and Thursday (14.2 ± 5.8, $p = 0.014$).

There were no differences between days in the average bout duration for time spent in walking based activity ($p > 0.05$); Figure 5-5), the average bout duration for time spent in sedentary behaviour ($p > 0.05$; Figure 5-5) peak cadence ($p > 0.05$; Figure 5-5) or the average 30-minute peak cadence ($p > 0.05$; Figure 5-5).

Given that there were very few differences between days, and that the one difference which was demonstrated was small, these variables were averaged across days

Table 5-2: Time spent in walking based activity and sedentary behaviour across each day that the SAM was worn, expressed in minutes, for participants with COPD (n = 30).

		Days							*p value*
	steps/min	Sunday *mean ± SD*	Monday *mean ± SD*	Tuesday *mean ± SD*	Wednesday *mean ± SD*	Thursday *mean ± SD*	Friday *mean ± SD*	Saturday *mean ± SD*	
Walking based activity (min)	≥ 1	156 ± 90	173 ± 69	169 ± 78	180 ± 74	177 ± 89	166 ± 88	172 ± 88	*0.61*
Sedentary behaviour (min)	0	613 ± 165	649 ± 84	614 ± 175	633 ± 113	625 ± 98	627 ± 101	613 ± 83	*0.76*
Total daily steps count		4223 ± 2928	4465 ± 2586	4071 ± 2063	4423 ± 2351	4267 ± 2614	3504 ± 2614	3916 ± 2461	*0.43*
Walking based activity in cadence bands (min)									
Incidental movement	1 to 19	90 ± 50	104 ± 36	102 ± 45	111 ± 32	109 ± 43	101 ± 44	104 ± 45	*0.52*
Sporadic movement	20 to 39	44 ± 29	48 ± 25	46 ± 25	47 ± 24	48 ± 24	43 ± 29	46 ± 22	*0.97*
Purposeful steps	40 to 59	15 ± 15	16 ± 11	14 ± 11	17 ± 11	16 ± 11	15 ± 16	15 ± 12	*0.83*
Slow walking	60 to 79*	3 (1 to 7)	5 (2 to 8)	3 (1 to 11)	4 (0 to 8)	3 (1 to 7)	2 (1 to 7)	4 (1 to 8)	*0.30*
Medium walking	80 to 99*	1 (0 to 3)	0 (0 to 0)	0 (0 to 3)	0 (0 to 1)	0 (0 to 2)	1 (0 to 1)	0 (0 to 3)	*0.47*
Brisk walking	100 to 119*	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	*0.37*
Faster locomotion	≥ 120*	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	*0.37*

Data are presented as mean ± standard deviation or *median (interquartile range). min: minutes; SD: standard deviation

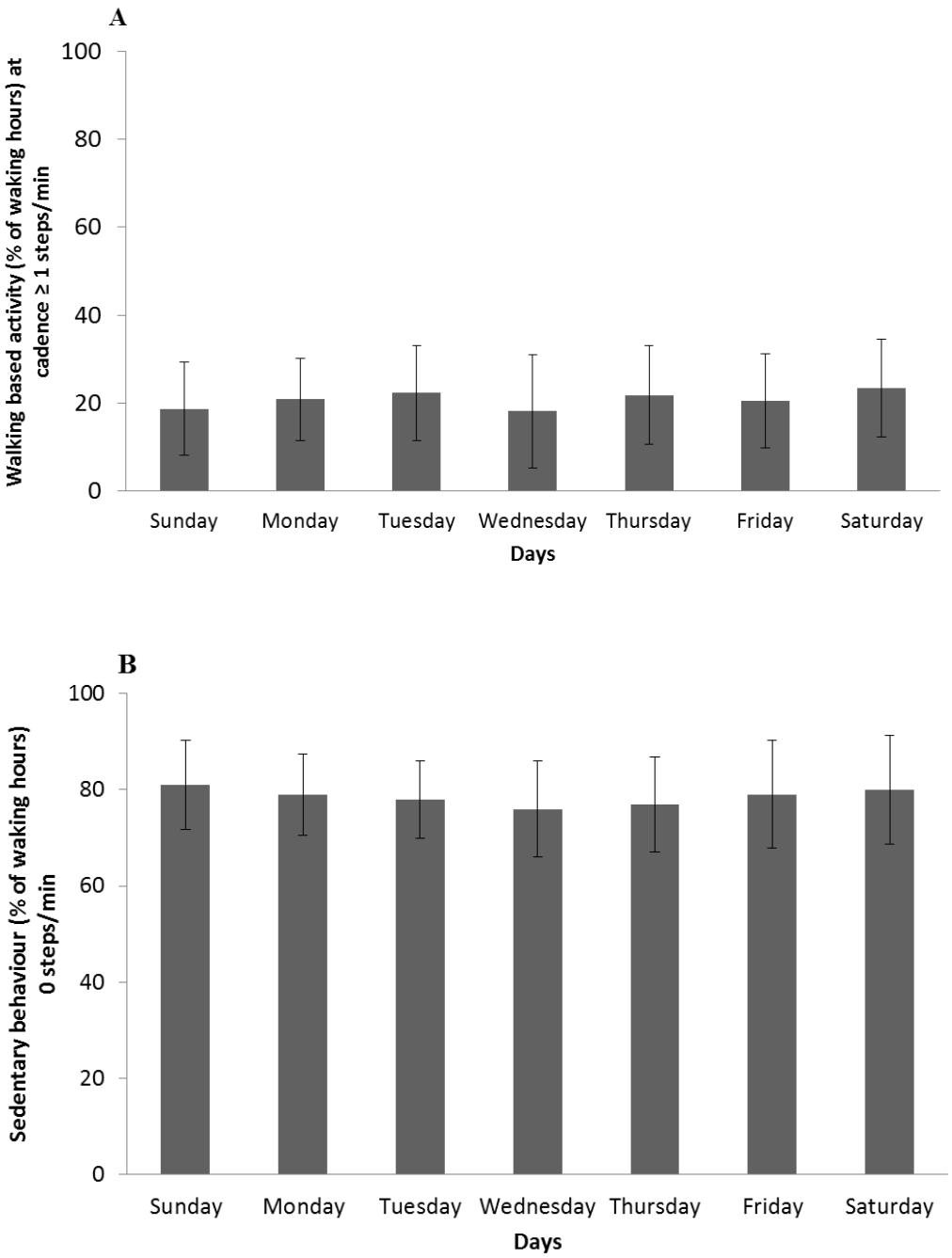

Figure 5-2: Time spent in walking based activity and sedentary behaviour across each day that the SAM was worn, expressed as a percentage of total wear time, for participants with COPD A) walking based activity and B) sedentary behaviour. Data are expressed as mean ± standard deviation.

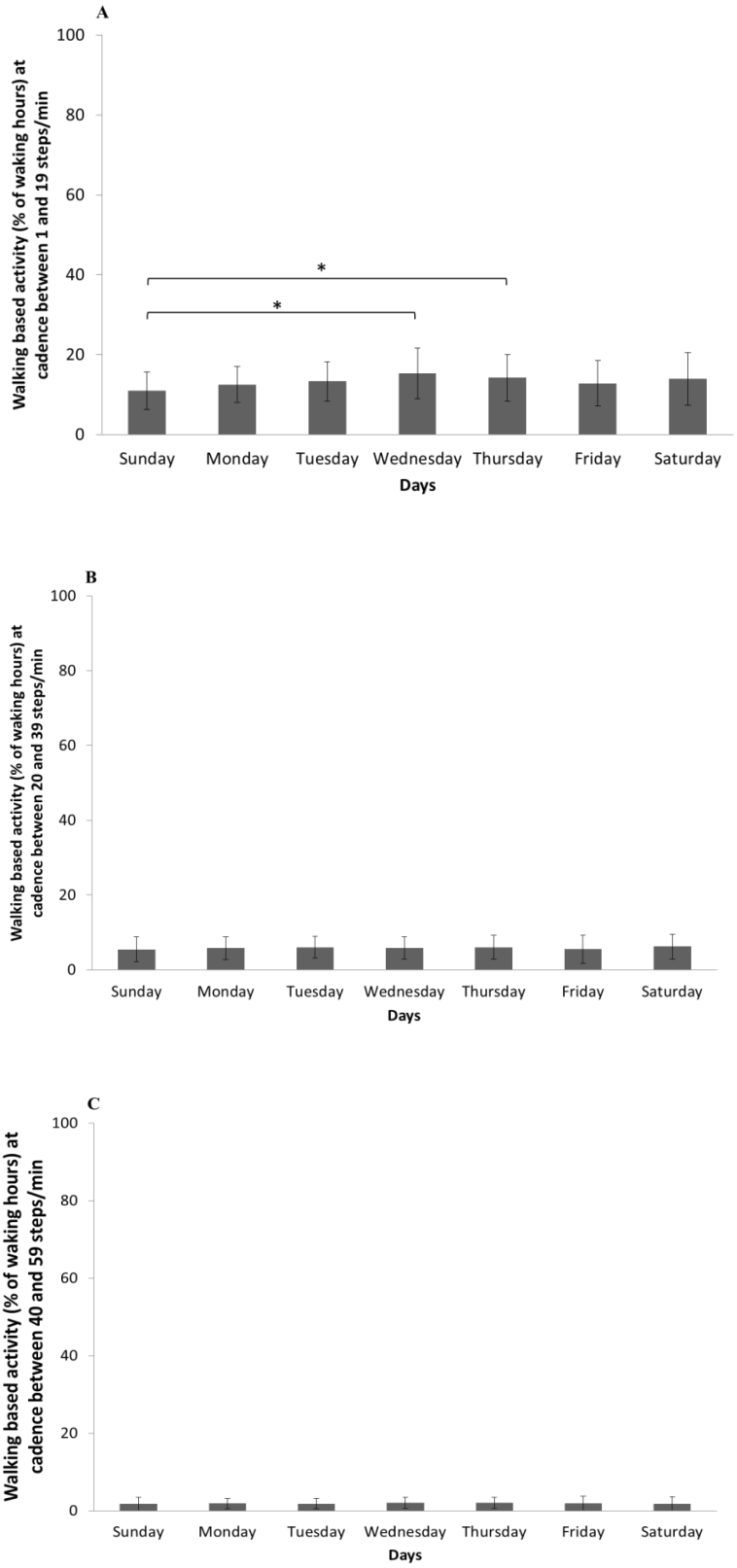

Figure 5-3: Time spent in walking based activity cadence of A) 1 to 19, B) 20 to 39 and C) 40 to 59 steps/day across each day that the SAM was worn, expressed as a percentage of total wear time, for participants with COPD A). Data are expressed as mean ± standard deviation. ****Statistically significant difference* **($p < 0.05$).**

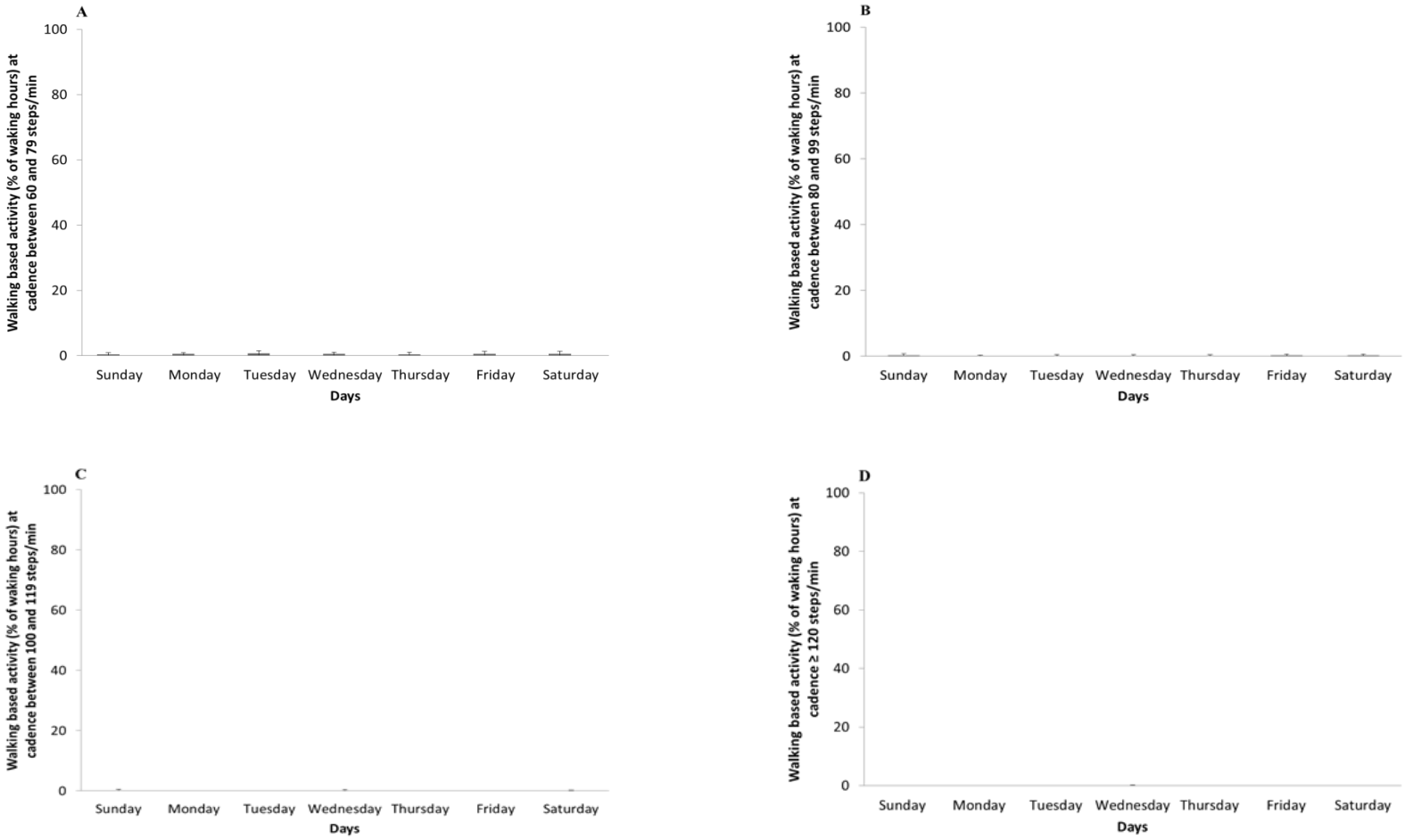

Figure 5-4: Time spent in walking based activity cadence of A) 60 to 79, B) 80 to 99, C) 100 to 119 and D) ≥ 120 steps/day across each day that the SAM was worn, expressed as a percentage of total wear time, for participants with COPD. Data are expressed as mean ± standard deviation.

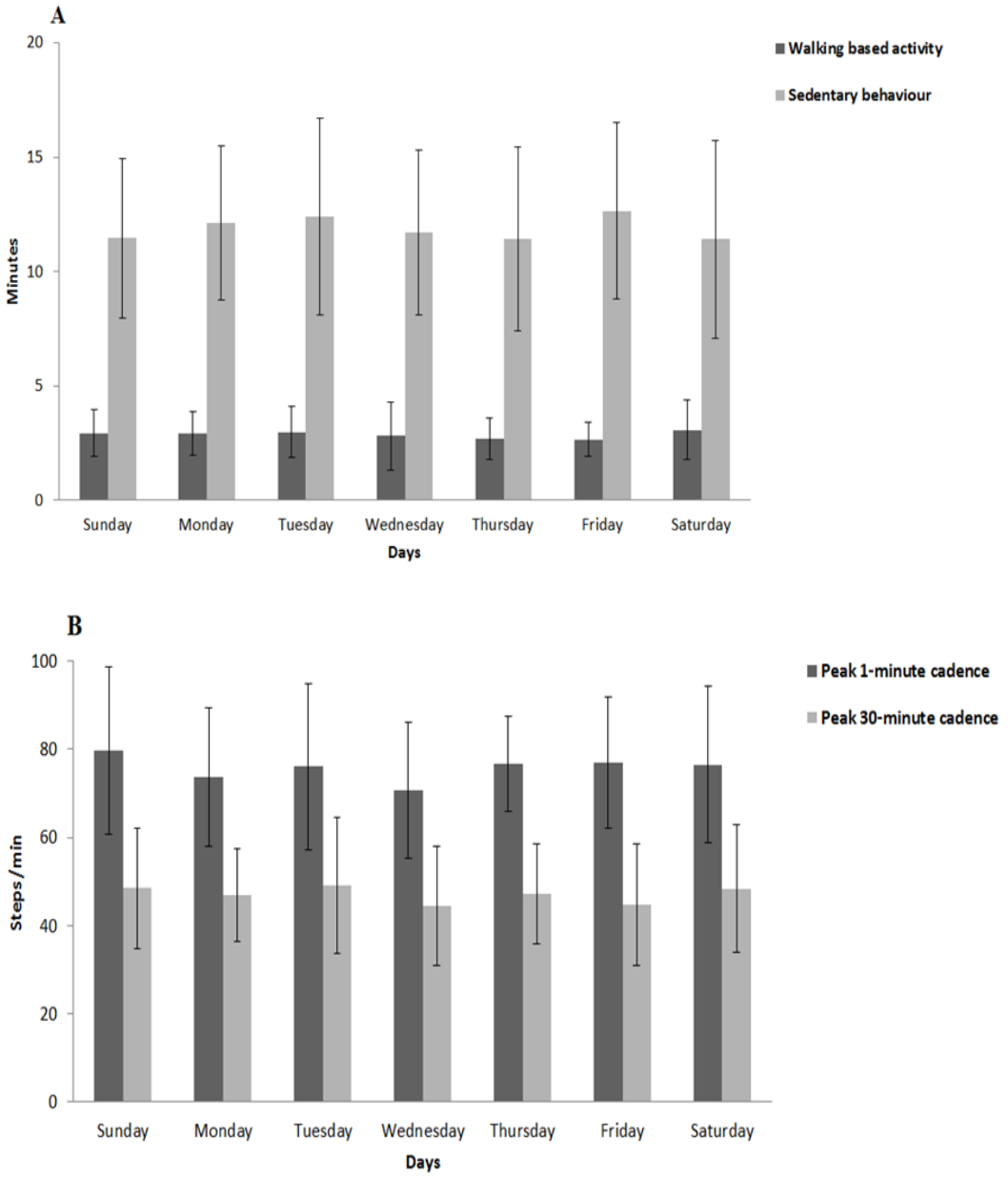

Figure 5-5: (A) Average bout durations for walking based activity and sedentary behaviour and (B) the peak and average 30-minute peak cadence across each day that the SAM was worn for participants with COPD. Data are expressed as mean ± standard deviation.

5.4.3.2 Healthy controls

There were no differences between days in the time spent in walking based activity and sedentary behaviour expressed as minutes (Table 5-2). There was a significant difference between days in the percentage of waking hours accumulated in walking based activity ≥ 1step/min ($p = 0.040$) (Figure 5-6). Post-hoc analyses revealed that the percentage of waking hours accumulated in walking based activity on Friday (32.0 ± 9.6) was lower than that measured on Sunday (34.8 ± 13.5, $p = 0.047$), Monday (36.8 ± 9.3, $p = 0.026$), Tuesday (37.4 ± 10.7, $p = 0.002$), Wednesday (39.8 ± 10.3, $p = 0.002$) and Thursday (36.8 ± 9.6, $p = 0.026$).

In healthy controls, there was a significant difference between days in the percentage of waking hours accumulated in walking based activity ≥ 1step/min ($p = 0.048$) (Figure 5-6). Post-hoc analyses revealed that the percentage of waking hours accumulated in walking based activity on Friday (32.3 ± 9.6) was lower than that measured on Sunday (35.0 ± 13.5, $p = 0.044$), Monday (36.8 ± 9.3, $p = 0.047$), Tuesday (37.4 ± 10.7, $p = 0.026$), Wednesday (38.8 ± 10.3, $p = 0.002$) and Thursday (36.9 ± 8.9, $p = 0.026$).

There was a significant difference between days in the percentage of waking hours accumulated in sedentary behaviour 0 steps/min ($p = 0.044$) (Figure 5-6). Post-hoc analyses revealed that the percentage of waking hours accumulated in sedentary behaviour on Friday (68.0 ± 9.5) was higher than that measured on Sunday (62.6 ± 9.3, $p = 0.046$), Monday (62.8 ± 9.5, $p = 0.028$), Tuesday (62.6 ± 11.1, $p = 0.017$), Wednesday (60.3 ± 10.7, $p = 0.002$) and Thursday (63.5 ± 8.1, $p = 0.040$).

No differences were observed between total daily step counts between days (Table 5-2). When walking based activity was divided into cadence bands and expressed in minutes (Table 5-3) or percentage of total wear time (Figure 5-7 and Figure 5-8), there was no difference between days ($p > 0.05$).

There were no differences between days in the average bout duration for time spent in walking based activity (($p > 0.05$); Figure 5-9), the average bout duration for time spent in sedentary behaviour ($p > 0.05$; Figure 5-9) peak cadence ($p > 0.05$; Figure 5-9) or the average 30-minute peak cadence ($p > 0.05$; Figure 5-9).

Given that there were very few differences between days, and that those differences which were demonstrated were small, these variables were averaged across days.

Table 5-3: Time spent in walking based activity and sedentary behaviour across each day that the Stepwatch™ Activity Monitor was worn, expressed in minutes, for healthy controls (n = 29).

		Days							*p value*
		Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	
	steps/min	*mean ± SD*	*mean ± SD*	*mean ± SD*	*mean ± SD*	*mean ± SD*	*mean ± SD*	*mean ± SD*	
Walking based activity (min)	≥ 1	304 ± 74	302 ± 91	308 ± 91	315 ± 97	302 ± 78	2861 ± 85	294 ± 88	*0.68*
Sedentary behaviour (min)	0	514 ± 92	510 ± 73	513 ± 105	499 ± 101	527 ± 88	545 ± 96	529 ± 115	*0.79*
Total daily steps count		7787 ± 2871	7965 ± 2889	7758 ± 2658	7358 ± 3155	7744 ± 2920	6752 ± 3498	6937 ± 3370	*0.38*
Walking based activity in cadence bands (min)									
Incidental movement	1 to 19	169 ± 55	166 ± 51	167 ± 58	170 ± 54	165 ± 55	152 ± 59	162 ± 53	*0.10*
Sporadic movement	20 to 39	86 ± 24	84 ± 34	90 ± 36	96 ± 47	83 ± 26	84 ± 29	90 ± 28	*0.15*
Purposeful steps	40 to 59	35 ± 15	36 ± 14	32 ± 14	33 ± 16	35 ± 12	34 ± 13	28 ± 9	*0.09*
Slow walking	60 to 79	12 ± 9	13 ± 8	13 ± 8	11 ± 8	13 ± 7	10 ± 5	9 ± 6	*0.18*
Medium walking	80 to 99*	2 (1 to 3)	0 (0 to 4)	2 (1 to 4)	2 (1 to 5)	2 (0 to 8)	2 (1 to 5)	2 (0 to 5)	*0.35*
Brisk walking	100 to 119*	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 1)	*0.25*
Faster locomotion	≥ 120*	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	*0.47*

Data are presented as mean ± standard deviation or *median (inter quartile range). min: minutes; SD: standard deviation.

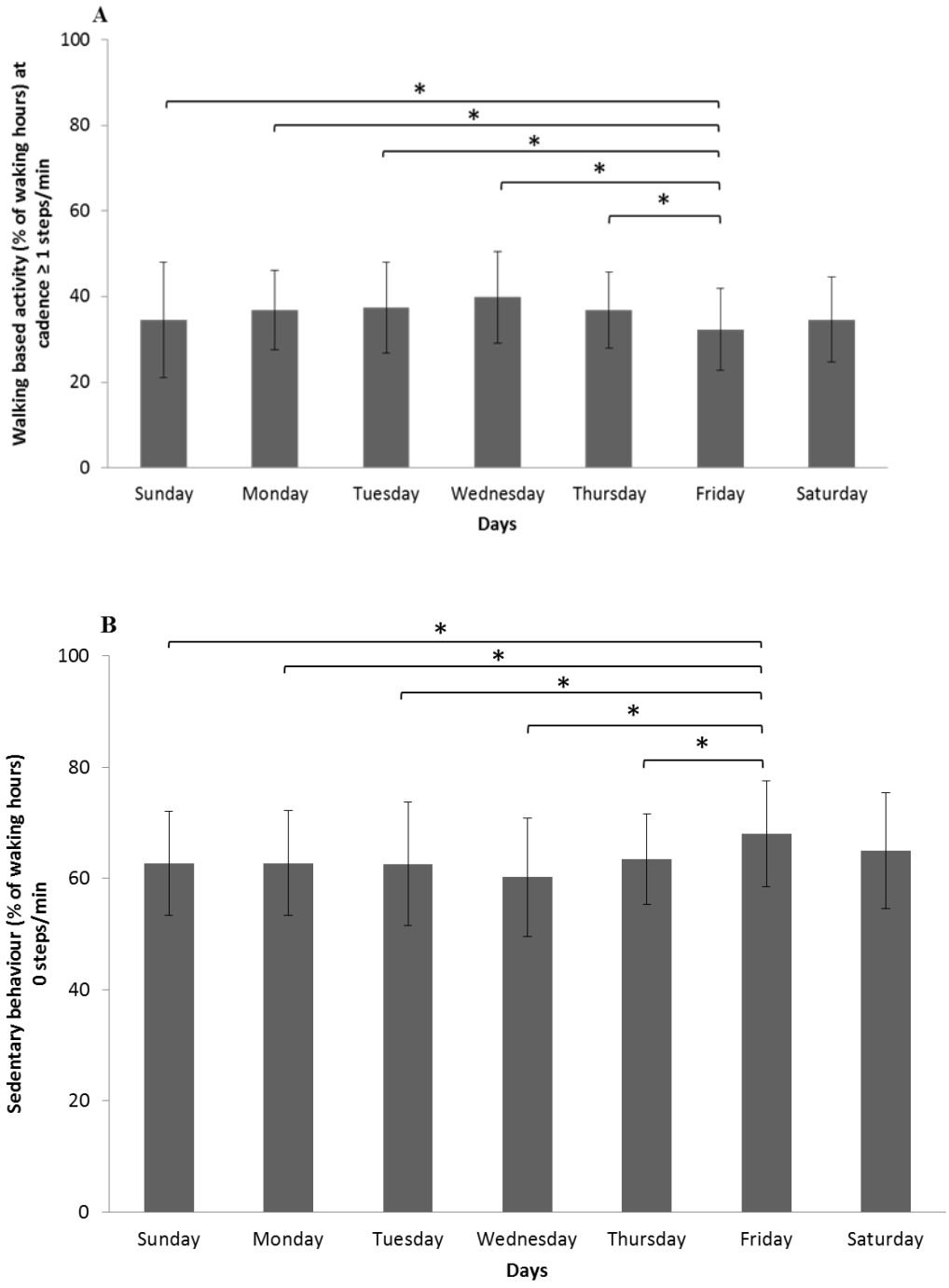

Figure 5-6: Time spent in walking based activity and sedentary behaviour across each day that the SAM was worn, expressed as a percentage of total wear time, for healthy controls A) walking based activity and B) sedentary behaviour. Data are expressed as mean ± standard deviation. ****Statistically significant difference* **($p < 0.05$).**

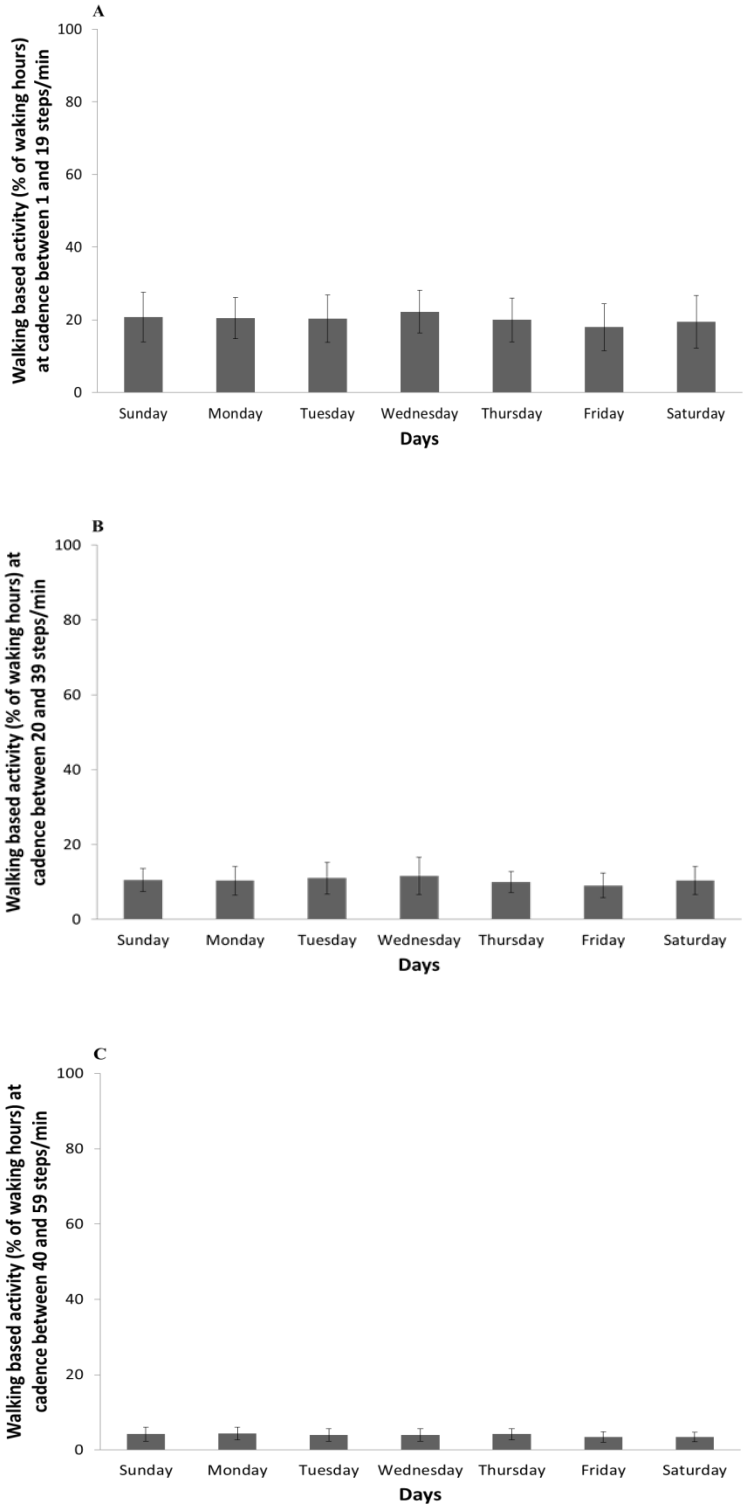

Figure 5-7: Time spent in walking based activity cadence of A) 1 to 19, B) 20 to 39 and C) 40 to 59 steps/day across each day that the SAM was worn, expressed as a percentage of total wear time, for healthy controls. Data are expressed as mean ± standard deviation.

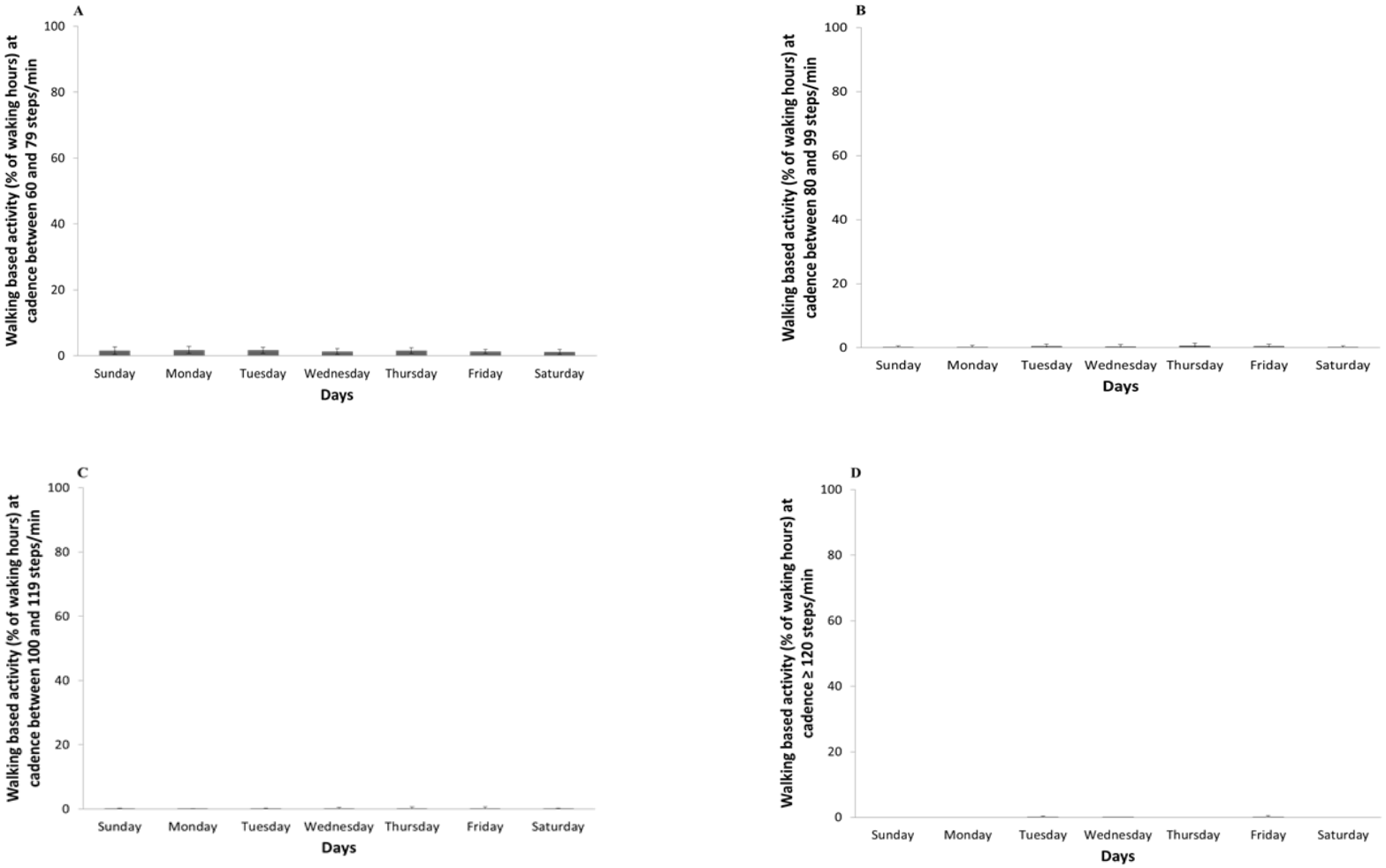

Figure 5-8: Time spent in walking based activity cadence of A) 60 to 79, B) 80 to 99, C) 100 to 119 and D) ≥ 120 steps/day across each day that the SAM was worn, expressed as a percentage of total wear time, for healthy controls. Data are expressed as mean ± standard deviation.

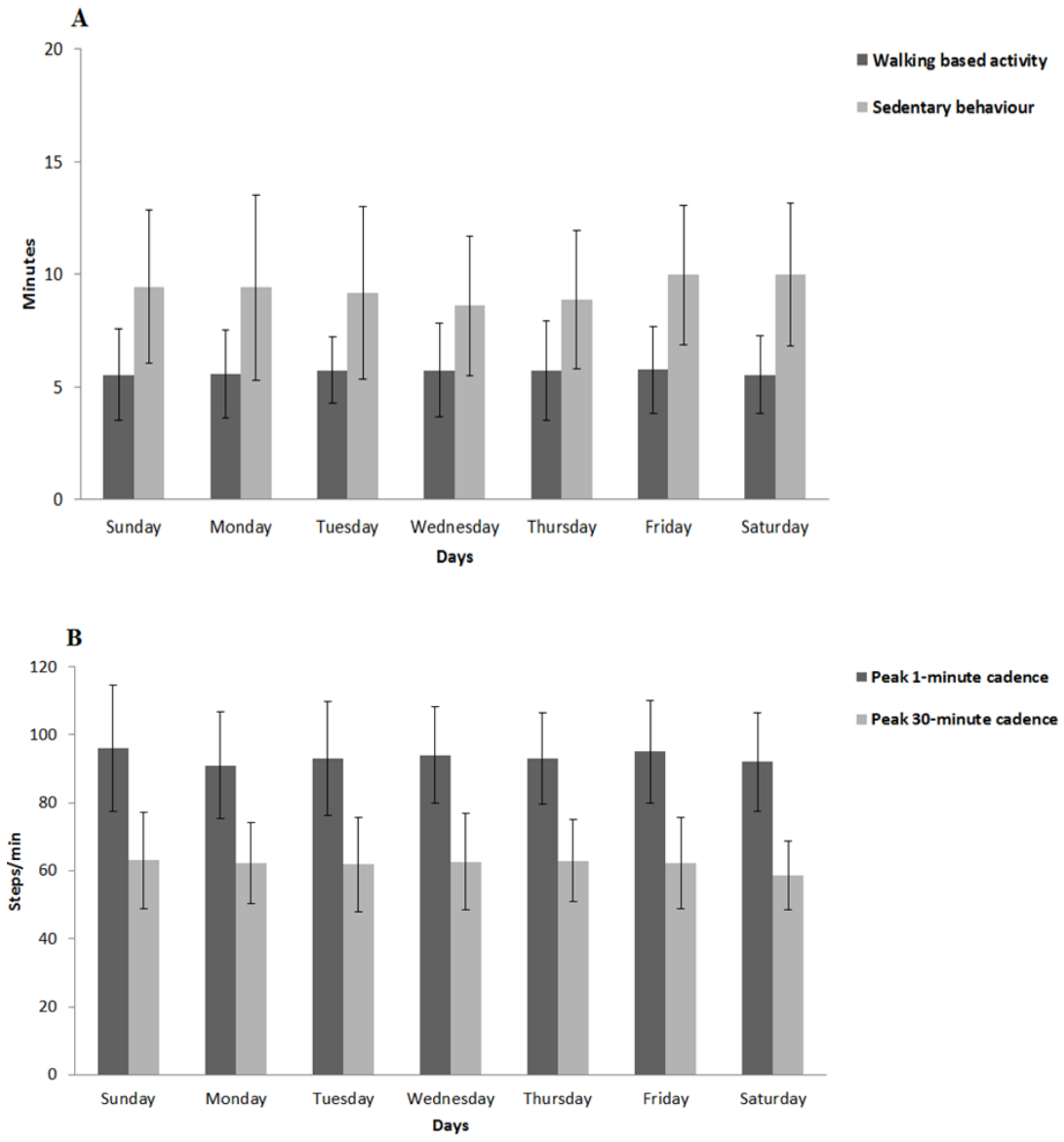

Figure 5-9: (A) Average bout durations for walking based activity and sedentary behaviour and (B) the peak and average 30-minute peak cadence across each day that the SAM was worn for healthy controls. Data are expressed as mean ± standard deviation.

5.4.4 Comparisons between participants with COPD and healthy controls of variables related to walking based activity and sedentary behaviour, averaged across the days that Stepwatch™ Activity Monitor data were available

5.4.4.1 Time spent in walking based activity and sedentary behaviour

Table 5-4 presents the average total time spent in walking based activity (≥ 1 step/min) and sedentary behaviour (0 steps/min) by participants with COPD and healthy controls expressed as minutes. Figure 5-10 presents the average total time spent in walking based activity (≥ 1 steps/min) and sedentary behaviour (0 steps/min) by participants with COPD and healthy controls, expressed as a percentage of waking hours. Compared with healthy controls, participants with COPD spent less time in walking based activity (37 ± 7% *versus* 22 ± 8% of waking hours; $p < 0.001$). This difference was equivalent to 15 ± 12% of waking hours, or 131 ± 105 minutes ($p < 0.001$).

Compared with healthy controls, participants with COPD spent more time in sedentary behaviour (63 ± 6% *versus* 78 ± 8% of waking hours; $p < 0.001$). This difference was equivalent to 15 ± 13% of waking hours, or 109 ± 103 minutes ($p < 0.001$).

5.4.4.2 Average daily step count

Compared to healthy controls, males with COPD accumulated fewer daily steps (7,472 ± 2,258 *versus* 4,124 ± 2,039 steps/day; $p < 0.001$).

5.4.4.3 Time spent in walking based activity undertaken at different cadences

Table 5-4 presents the average total time spent in walking based activity undertaken at the different cadence bands. Compared with healthy controls, participants with COPD spent fewer minutes (Table 5-4) and a lower percentage of waking hours (Figure 5-10) in walking based activity at all cadence bands < 100 steps/min. No differences were seen between participants with COPD and healthy controls in the time spent at cadence bands ≥ 100 steps/min, expressed as minutes (Table 5-4) or as a percentage of waking hours (Figure 5-10) ($p > 0.05$).

Table 5-4: Comparison of walking based activity, divided into cadence bands in both participants with COPD and healthy controls, expressed in minutes.

	steps/min	COPD participants *mean ± SD*	Healthy controls *mean ± SD*	*p value*
Walking based activity (min)	≥ 1	170 ± 58	302 ± 53	*< 0.001**
Sedentary behaviour (min)	0	629 ± 80	520 ± 60	*< 0.001**
Total daily steps count		4124 ± 2039	7472 ± 2258	*< 0.001**
Walking based activity in cadence bands (min/day)				
Incidental movement	1 to 19	104 ± 29	164 ± 33	*< 0.001**
Sporadic movement	20 to 39	46 ± 20	87 ± 21	*< 0.001**
Purposeful steps	40 to 59	14 ± 10	34 ± 9	*< 0.001**
Slow walking	60 to 79	5 ± 4	12 ± 4	*< 0.001**
Medium walking	80 to 99	1 ± 2	4 ± 3	*0.008**
Brisk walking	100 to 119	0 ± 1	1± 1	*0.163*
Faster locomotion	≥ 120	0 ± 0	0 ± 1	*0.400*

Data are presented as mean ± standard deviation. min: minutes; SD: standard deviation. * *Significant difference between groups.*

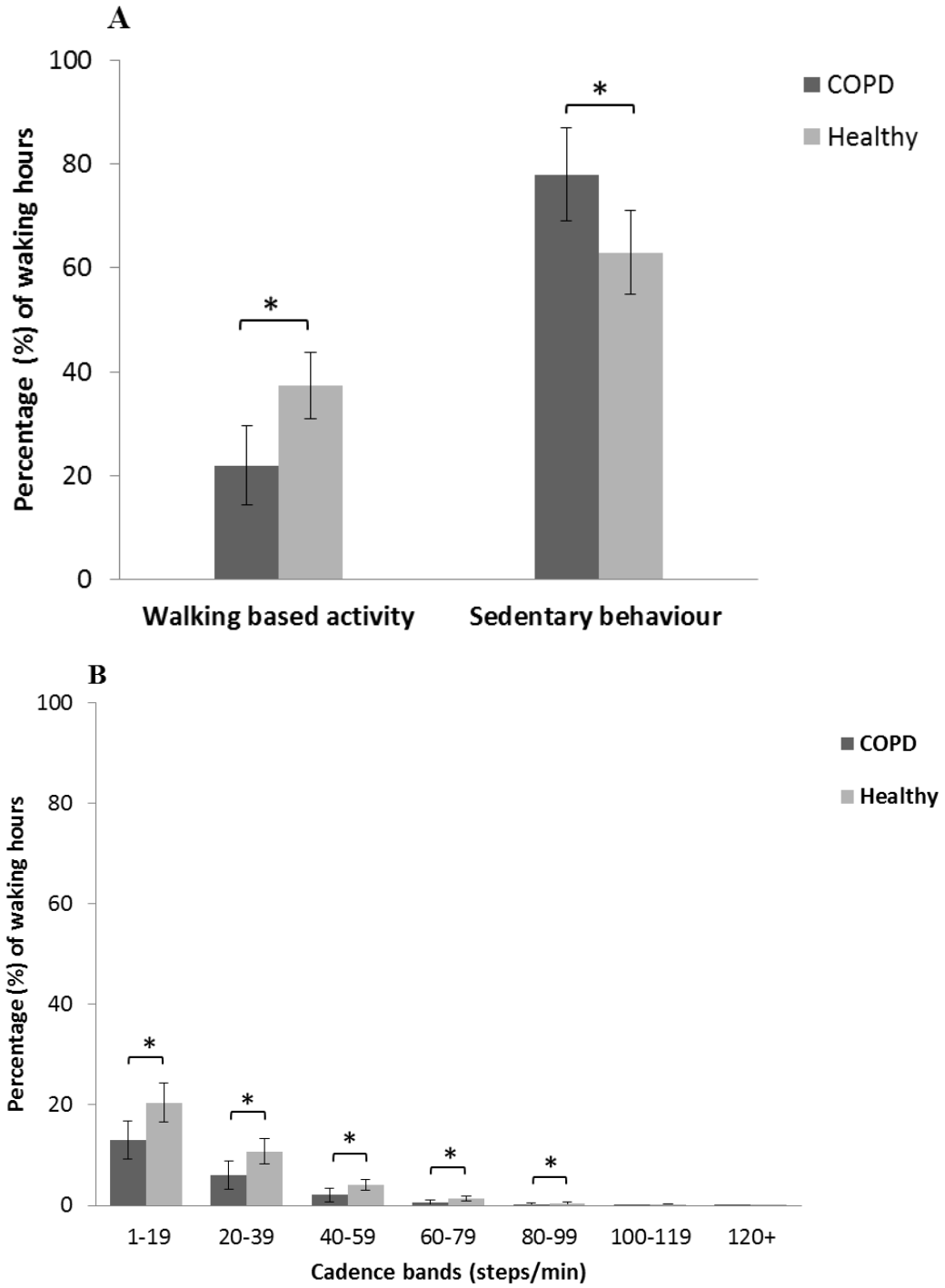

Figure 5-10: Comparison of A) walking based activity and sedentary behaviour and B) walking based activity, divided into cadence bands in both participants with COPD and healthy controls, expressed as a percentage of waking hours. Data are expressed as mean ± standard deviation. ****Statistically significant difference* **($p < 0.05$).**

5.4.5 Patterns of accumulation for both walking based activity and sedentary behaviour

Figure 5-11 illustrates the average duration of bouts for walking based activity and sedentary behaviour in participants with COPD and healthy controls. Compared with healthy controls, participants with COPD accumulated time in walking based activity in shorter bouts (6 ± 1 *versus* 3 ± 1 min/day; $p < 0.01$) and sedentary behaviour in longer bouts (9 ± 2 *versus* 12 ± 2 min/day; $p < 0.01$).

5.4.6 Peak and 30-minute peak cadences for walking based activity

Figure 5-11 demonstrates the peak and average 30-minute peak cadence in participants with COPD and healthy controls. The peak cadence was lower in participants with COPD than healthy controls (76 ± 13 *versus* 93 ± 13 steps/min; $p < 0.01$). The average 30-minute peak cadence was lower in participants with COPD compared with healthy controls (47 ± 11 *versus* 62 ± 9 steps/min; $p < 0.01$).

5.4.7 The proportion of participants who met the criteria for participating in sufficient walking based activity

Compared with healthy controls, the proportion of participants with COPD who met the criteria for participating in sufficient walking based activity (7,000 steps per day for five or more days) was lower (34 % *versus* 7%; $p < 0.001$).

5.4.8 Associations between the components of Dyspnoea-12 questionnaire with time spent in walking based activity and sedentary behaviour

Moderate associations were demonstrated between the score for the quality component of the D-12 and time spent in walking based activity, expressed as minutes and percentage of waking hours (all $r \geq -0.52$, $p < 0.01$). Similarly, moderate associations were demonstrated between the score for the quality component of the D-12 and time spent in sedentary behaviour, expressed as minutes and percentage of waking hours (all $r \geq 0.46$, $p < 0.01$). Strong associations were revealed between the score of the emotional response component of the D-12 and time (expressed as minutes and percentage of waking hours) spent in walking based activity (all $r \geq -0.63$, $p < 0.01$) and sedentary behaviour (all $r \geq 0.66$, $p < 0.01$). The total scores of the D-12 were strongly associated with time (expressed as and minutes and

percentage of waking hours) spent in walking based activity (all $r \geq -0.72$, $p < 0.01$) and sedentary behaviour (all $r \geq 0.66$, $p < 0.01$).

Figure 5-11: Comparison of the bout duration for walking based activity and sedentary behaviour in both participants with COPD and healthy controls. Data are expressed as mean ± standard deviation. ****Statistically significant difference* **($p < 0.05$).**

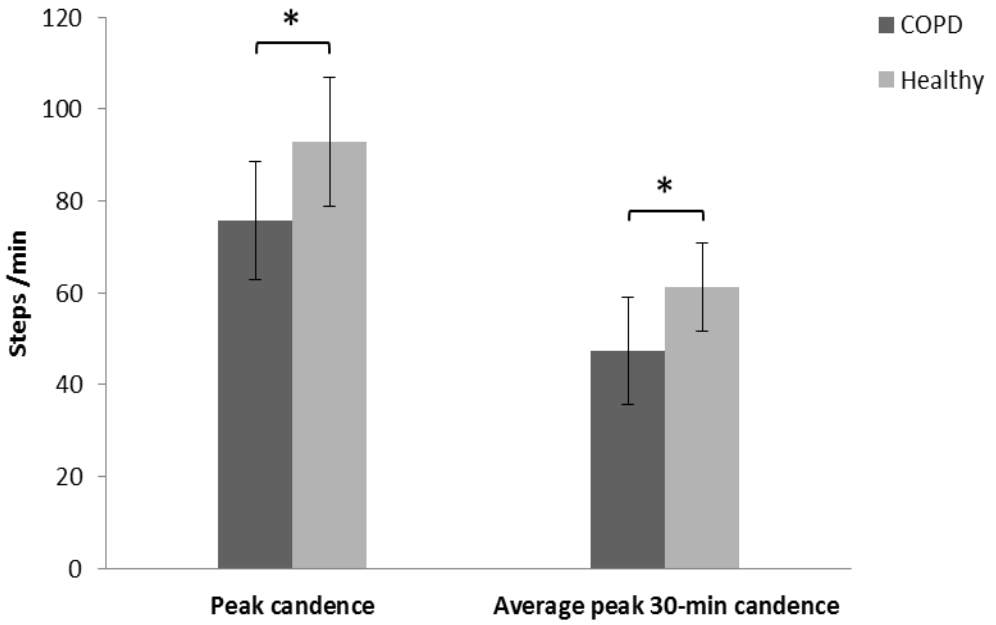

Figure 5-12: Comparison of the peak and average peak 30-minute cadences in both participants with COPD and healthy controls. Data are expressed as mean ± standard deviation. ****Statistically significant difference* **($p < 0.05$).**

5.5 Discussion

This study demonstrated several differences between males with COPD and healthy controls in Saudi Arabia in terms of time spent in walking based activity and sedentary behaviour, total daily steps count, the duration of bouts spent in walking based activity and sedentary behaviour as well as peak intensity of walking based activity. The results demonstrate that males with COPD spent less of their waking hours in walking based activity and more time in sedentary behaviour when compared with healthy controls. In addition, males with COPD accumulated fewer steps in their daily life compared to healthy controls. Further, males with COPD, on average, accumulated walking based activity in shorter bouts and sedentary behaviour in longer bouts when compared with healthy controls. The highest peak and average 30-minute cadences were lower in males with COPD compared to that observed in the healthy controls. The results of this study also demonstrated that the proportion of males with COPD who participated in sufficient physical activity was lower than that seen in healthy controls. In addition, this study demonstrated moderate to strong associations between the quality and emotional response components of the D-12 with time spent in walking based activity and sedentary behaviour in COPD.

5.5.1 Walking based activity and sedentary behaviour

Earlier work reported that two days of measurement (weekdays only) were sufficient to reliably assess daily physical activity, defined as an intra-class coefficient ≥ 0.7 (56). Subsequent studies have suggested that the minimum number of wear days depends on factors such as disease severity (82, 85). Watz et al (85) demonstrated that up to five days of measurement was necessary for reliable results of physical activity in people with mild COPD, while those with more severe COPD required only two to three days. Given that the participants in the present study had moderate to very severe COPD, a minimum of five days of wear time was required to include the data in this study's analyses.

This is the first study to report data on walking based activity and sedentary behaviour in males with COPD in Saudi Arabia, and to compare it with healthy controls in Saudi Arabia. The current study demonstrated that, compared to healthy

controls, males with COPD spent 15 ± 12% less of their waking hours in walking based activity and 15 ± 13% more of their waking hours in sedentary behaviour. These findings correspond to previously reported work conducted in Belgium and Brazil (56, 57). The number of daily steps found in this study for males with COPD (4,124 ± 2,039 steps/day) was similar to that reported in people with COPD from Canada (4,378 ±2,105 steps/day) (463) and the Netherlands (4,472 ±2,716 steps/day) (464). Moy et al (465) showed that, people with COPD who did not walk much had an increased risk of acute exacerbations of COPD and hospital admission. Thus, the implications of the results of this study, whereby low levels of physical activity were seen, are that these males with COPD may be at higher risk of acute exacerbation and hospitalisation.

This is the first study to report the proportion of males with COPD and healthy controls in Saudi Arabia who met the criteria for participating in sufficient walking based activity. Compared to healthy controls, the proportion of males with COPD (7%) who accumulated an average of ≥ 7,000 in five or more days was lower than that for healthy controls (34%). These findings increase the importance of designing interventions aiming at increasing daily steps in males with COPD to meet the recommended amount of physical activity necessary to promote and maintain health.

Males with COPD in this study were more sedentary, with a higher proportion (78%) of their waking hours spent in sedentary behaviour, than that reported in people with COPD from Belgium (64%) and Brazil (56%) (56, 57). The discrepancy between the present study and the previous studies in terms of the percentage of waking hours spent in sedentary behaviour may reflect ethnic, geographical, environmental, cultural and lifestyle factors unique to Saudi Arabia that can impact participation in physical activity. In addition, it is important to note that the discrepancy may also have been due to the use of different activity monitors between the studies as well as different definitions used for sedentary behaviour (56, 57). In the present study, the SAM was used to measure steps count and a pragmatic cut-off of 0 steps/min was defined as sedentary behaviour. In the studies on people with COPD from Belgium and Brazil (56, 57), the Dynaport accelerometer (McRoberts BV, The Hague, Netherlands) was used to quantify the time spent in sedentary behaviour which was defined as the time spent in a sitting or reclining posture (56, 57). Notwithstanding

these differences, the magnitude of difference between males with COPD and healthy controls from Saudi Arabia in terms of the percentage of waking hours spent in sedentary behaviour (15%) was similar to that reported in Belgium in those with COPD (18%) when compared to their healthy controls (56). The findings of this study reinforce the importance of implementing interventions aim at increasing time spent in walking based activity by decreasing time in sedentary behaviour in males with COPD.

In the present study, there were differences across days in the percentage of wear time spent in walking based activity and sedentary behaviour by healthy controls. These differences were revealed between Friday and the other days of the week. This discrepancy could be explained as Friday is considered a holy day for Muslims and they spend much of their time in the mosque reading and praying.

5.5.1.1 Time spent in walking based activity undertaken at different cadences

This is also the first study to report data on the time spent walking at different cadences by males with COPD. In the current study, males with COPD spent less time (expressed as a percentage of waking hours and minutes) walking at cadences < 100 steps/min, when compared to healthy controls. High cadences (≥ 100 steps/min) have been considered the threshold for moderate intensity physical activity in adults (466). Therefore, it is important to spend time in accumulating steps at cadences ≥ 100 steps/min, as moderate physical activity is recommended by the ACSM guidelines to optimise health benefits such as reductions in the risk of cardiovascular and metabolic disease (54). However, neither males with COPD nor the healthy controls in this study participated in walking based activity at cadences ≥ 100 steps/min, which explains the lack of differences between these two groups at high cadences. These findings suggest that males with COPD as well as healthy controls in Saudi Arabia may be at greater risk of developing chronic diseases, such as cardiovascular and metabolic diseases, as they do not spend time participating in daily moderate intensity physical activity (54). Therefore, in Saudi Arabia, awareness of the benefits of walking at a moderate intensity needs to be promoted among the general public as well as males with COPD. Studies that reported changes in physical activity in people with COPD have frequently used individual goal setting, collection of objective physical activity data in order to place goals and/or provide feedback,

overcome barriers, encourage adherence, motivational interviewing and regular contact with healthcare professionals to increase motivation (467-472). Therefore, these approaches need to be considered, in Saudi nationals, when implementing interventions to increase time of participation in physical activity and reduce time in sedentary behavior.

In a comparison with data reported by the NHANES (67) on time spent (expressed as a percentage of waking hours) at different cadences by healthy males from the United States of America, healthy males in this study spent less time at both cadences < 100 steps/min (21% versus 67%) and ≥ 100 steps/min (1% versus 6%). Furthermore, healthy controls in the present study were more sedentary, with a higher proportion of their waking hours (63%) spent in sedentary behaviour than that (34%) reported by the NHANES (67). The discrepancy between the present study and the NHANES in terms of the percentage of waking hours spent in walking based activity at different cadences and in sedentary behaviour may reflect ethnic, geographical, environmental, cultural and lifestyle factors unique to Saudi Arabia that can influence participation in physical activity.

5.5.2 Patterns of accumulation for walking based activity and sedentary behaviour

This study is the first to report data on bout durations for walking based activity and sedentary behaviour in males with COPD in Saudi Arabia, and to compare this with healthy controls. The present study demonstrated that, compared to healthy controls, males with COPD accumulated time in walking based activity in shorter bouts and sedentary behaviour in longer bouts. The ACSM guidelines recommend that physical activity should be accrued in bouts of at least 10 minutes duration to optimise health benefits (54). However, the results of this study demonstrated that, on average, males with COPD did not meet these recommendations as they performed their activities in shorter bouts (≤ 3 min). This contrasts with earlier work by Donaire-Gonzalez et al (446), who investigated the pattern of accumulation of physical activity in 177 (94% males) people with COPD (age 71 ± 8 years; FEV_1 52 ± 16% predicted). The authors found that a relatively high proportion (60%) of people with COPD performed their physical activity in bouts ≥ 10 minutes. However, the study by Donaire-Gonzalez et al (446) used different methods than those used in the current study in terms of an

activity monitor and bout definition. They used a metabolic monitor (SenseWear® Pro2 Armband) that estimates energy expenditure, and defined physical activity bouts as any period ≥10 minutes at an intensity ≥ 1.5 METs per minute each day. Whereas, the present study used the SAM and defined walking based activity bouts as any period of time accrued in cadences ≥ 1 steps/min each day. Therefore, due to different methods, it is difficult to compare the results of this study with those reported by Donaire-Gonzalez et al (446).

In the present study, the bout duration for sedentary behaviour in males with COPD was longer than that seen in healthy controls. Longer duration in sedentary behaviour has been associated with deleterious health outcomes such as an increased risk of developing cardiovascular and metabolic diseases (401). Therefore, the clinical recommendation that can be taken for this is that people with COPD need to break up their sedentary behaviour with light intensity physical activity (e.g. standing up) more often. The bout durations in the present study for males with COPD and healthy controls were heavily influenced by a large number of bouts equal to one minute in duration. Despite this limitation, a difference in bout durations between males with COPD and healthy controls was evident.

It is likely that the impairment in exercise capacity demonstrated in people with COPD(56) affects the way they accumulate time in both walking and sedentary behaviour, such that they accumulate time in these domains in short bouts for walking based activity and long bouts for sedentary behaviours. These findings highlight the importance to educate males with COPD to spend a longer time in bouts of physical activity and a shorter time in bouts of sedentary behaviour for the purpose of health benefits such as reducing the risk of developing cardiovascular and metabolic disease (54, 61, 359).

5.5.3 Peak intensity of walking based activity

The peak and average 30-minute peak cadences were lower in males with COPD when compared to their healthy controls. This reduction in peak intensity of walking based activity in males with COPD may reflect their limitation of peak aerobic capacity (463). In addition, these findings suggest that males with COPD may have less capacity to walk at moderate intensity. A recent study in young adults (aged 22 ±

3 years) demonstrated that an average 30-minute peak cadence ≥ 102 steps/min was associated with better leg vascular compliance (473). Thus, if these results can be extrapolated to males with COPD, as in the present study, they may be at risk of developing leg vascular stiffness as they had a low average 30-minute peak cadence (47 steps/min).

In the present study, the average 30-minute peak cadence accrued by healthy controls in this study is somewhat lower than obtained for males in the United States of America (62 *versus* 74 steps/min) (462). This difference in the average 30-minute peak cadence of walking based activity due to variations in geographical location, ethnicity and lifestyle factors between populations. In addition, these differences demonstrate the importance of obtaining local 'healthy' control data.

5.5.4 Associations between the quality and emotional response components of the Dyspnoea-12 questionnaire and time spent in sedentary behaviour and walking based activity

Associations of moderate strength were demonstrated between the quality component of the D-12 with the time spent in walking based activity ($r \geq -0.52$) and sedentary behaviour ($r \geq 0.46$). However, the emotional response component of the D-12 yielded somewhat stronger associations with the time accumulated in walking based activity ($r \geq -0.63$) and sedentary behaviour ($r \geq 0.66$). The results of this study extend the validity of the Arabic language version of the D-12 in people with COPD (presented in Chapter 3) by showing the associations between the perception of dyspnoea and time spent in physical activity and sedentary behaviour. The associations found in this study indicate that males who spend a low proportion of their time in walking based activity also experience a greater emotional response to dyspnoea. This finding highlights the importance of targeting interventions that aim to minimise the emotional response to dyspnoea, as a strategy to optimise participation in physical activity and reduce the time spent in sedentary behaviour. Alternatively, interventions that optimise participation in physical activity may have a favourable impact on the emotional response to dyspnoea. However, the coefficient of determination for the association between emotional response to dyspnoea and the time spent in walking based activity ($R^2 = 0.40$) or sedentary behaviour ($R^2 = 0.44$) demonstrates that, at most , only 44% of variance in either time spent in walking

based activity or sedentary behaviour is explained by the emotional repose to dyspnoea. Therefore, this finding suggests that other important factors contribute to how males with COPD spend their daily time in walking based activity and sedentary behaviour.

5.6 Limitations

This study had a number of limitations which need to be considered. This study included a small sample and only recruited at a single location in Riyadh, Saudi Arabia. However, adequate power was used in this study and the minimum number of participants for completing this study was obtained for both groups. In addition, since the sample only included males, the results cannot be generalised to the female population. A large sample including males and females from different regions in Saudi Arabia is highly recommended to measure the level of physical activity and sedentary behaviour in Saudi nationals with COPD and their healthy controls. The cadence bands used in this study, which proposed by the NHANES (67), could be consider a limitation as it has not been validated in COPD population. However, these cadence bands, albeit somewhat arbitrary, appear to be appropriate to use in people with COPD. This can be stated because studies that have measured step counts in people with COPD, after instruction to walk at a medium pace, have recorded step counts between 73 and 79 steps/min (373, 377). Likewise, step counts for people after instruction to walk at slow pace have recorded step counts between 85 and 96 steps/min (377) and these cadences were similar to those used by the NHANES (67). Another limitation was that the present study only measured walking based activity and there are other forms of physical activity such as cycling, although cycling is uncommon in Saudi Arabia (474). However, walking is considered fundamental to human functioning and mobility. Furthermore, walking continues to be the most commonly reported leisure time physical activity (475).

5.7 Conclusions

Compared to healthy controls, males with COPD: (i) spent a lower proportion of their time in walking based activity and a higher proportion of their time in sedentary behaviour, (ii) spent shorter bouts in walking based activity and longer bouts in sedentary behaviour, (iii) accumulated fewer daily steps, (iv) had a lower proportion

meeting the criteria for participating in sufficient walking based activity and (v) had lower peak and average 30-minute peak cadences. The quality and emotional response components of the D-12 were associated with walking based and sedentary behaviour activity in males with COPD. In Saudi Arabia, there is a need to promote awareness of the health benefits of walking at moderate intensity among the general public as well as in males with COPD. In addition, strategies aimed at minimising the severity of dyspnoea and the emotional response to the sensation may reduce the time spent in sedentary behaviour and optimise participation in daily life activity in COPD. Alternatively, strategies aimed at increasing physical activity may reduce the severity of dyspnoea and the emotional response to dyspnoea in people with COPD.

CHAPTER 6

SUMMARY AND CONCLUSIONS

There were three studies undertaken in this program of research. Study 1 (chapter 3) sought to answer the following question;

> Is the Arabic version of Dyspnoea-12 questionnaire (D-12) reliable and valid in Saudi nationals with chronic obstructive pulmonary disease (COPD)?

Study 2 (chapter 4) sought to answer the following question:

> Do the quality and emotional response components of the D-12 differ between periods of with an acute exacerbation of COPD (AECOPD) and periods of clinical stability?

Study 3 (chapter 5) sought to answer the following questions:

1. Do physical activity and sedentary behaviour in males with COPD differ from those of healthy controls?

2. Are the quality and emotional response components of the D-12 associated with physical activity and sedentary behaviour in males with COPD?

This chapter synthesises the novel findings from this body of work, describes the clinical implications and suggests areas for further work.

6.1 The Arabic language version of the Dyspnoea-12 questionnaire: a reliable, valid and responsive measure of dyspnoea for use in the Gulf region

This program of research has translated the D-12 into the Arabic language. This is important given that there is little work on the measurement of dyspnoea of people with COPD in Saudi Arabia. The work completed in the program of research will facilitate the use of the D-12 and provide clinicians and researchers with a way of evaluating dyspnoea in people with COPD who speak in the Arabic language. This may lead to greater advocacy for programs such as pulmonary rehabilitation which

aim to reduce dyspnoea in people with COPD. The Arabic version of the D-12 can be used by researchers in those with asthma, and interstitial lung disease (ILD), populations for whom the D-12 has been previously validated in the English language (40, 41). However, this may require further studies to confirm the measurement properties of the D-12 in those populations who speak the Arabic language.

Data presented across the three studies completed in the program of research contribute novel information pertaining to the measurement properties of Arabic language version of the D-12. This is summarised below.

6.1.1 Reliability

Data presented in Chapter 3 demonstrated that the D-12 was reliable when administered on two occasions, separated by two weeks. This was demonstrated by the high intraclass correlation coefficient (ICC) (0.94) and excellent weighted kappa score (0.83). The reliability of the Arabic version of the D-12 were consistent with what were demonstrated in an English language in people with COPD (23). In addition, the total scores for 10 of the D-12 items were no different between the two administrations and the scores for the remaining two D-12 items differed by less than one point. Further, the scores obtained on the D-12 for people who were grouped according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades were reliable, as indicated by the ICC values ≥ 0.85 for GOLD grades 2 to 4. This is the first study to demonstrate the D-12 provided a stable measure of dyspnoea for people with moderate to very severe COPD.

6.1.2 Validity

The Arabic version of the D-12 presented in Chapter 3 was valid in a population of Saudi nationals with COPD, as significant associations were revealed between the D-12 components and its total score with the scores of questionnaire-based assessments. Specifically, a moderate to strong association was demonstrated between the D-12 total score and the score of COPD Assessment Test (CAT) questionnaire, which assessed health status, the total score of the Chronic Respiratory Disease Questionnaire (CRDQ), which assessed health-related quality of life, (all $r \geq 0.50$; $p < 0.01$). These data were consistent with early work in people with COPD

(23). In addition, data supporting the validity of the D-12 was also presented in Chapter 5, which demonstrated a moderate to strong association between the quality and emotional response components of the D-12 as well as the total score of the D-12 with time spent in walking based activity and the accumulation of time spent in sedentary behaviour (r = -0.52 and 0.46, respectively, all $p < 0.01$). This is the first study to report associations between the D-12 and a common form of physical activity, such as walking, and sedentary behaviour in people with COPD. People with COPD become more sedentary and less physically active and the main reason for that is dyspnoea during exertion. Therefore, it is expected that dyspnoea has a relationship with physical activity and sedentary behaviour. These findings may stimulate future research into ameliorating the emotional response of dyspnoea, which appears to have the greatest adverse effect on participation in physical activity and the accumulation of time in sedentary behaviour.

The findings of this research also reported data showing the capacity of the D-12 to discriminate between people grouped according to their disease severity (Chapters 3 and 4). Data presented in Chapter 3 demonstrated the capacity of the D-12 to discriminate between people with moderate and very severe COPD. These findings were confirmed and expanded in Chapter 4. Data in Chapter 4 demonstrated that the D-12 has the capacity to discriminate between people with moderate and very severe COPD during hospitalisation for an acute exacerbation of COPD and when they had returned to clinical stability. These findings provide additional evidence of the validity of the D-12, as dyspnoea has been shown previously to worsen with advancing disease (476).

6.1.3 Responsiveness

Data presented in Chapter 4 demonstrated that the D-12 was responsive to change in dyspnoea. Of note, this is the first study to explore and demonstrate the responsiveness of the D-12 in any language in terms of interventions or changes in clinical status. Specifically, the quality and emotional response components of the D-12 were responsive to a change in clinical status. This was indicated by the large effect sizes (≥ 1.6) that were obtained for the components and the total score of the D-12 between periods of an AECOPD and clinical stability. The responsiveness of the D-12 was less that of the CAT (effect sizes 2.1 *versus* 3.0). The most reason for

that is the CAT comprises items related to a broad range of factors that are likely to be adversely impacted during an AECOPD such as sleep quality and energy levels, rather than just dyspnoea. However, the responsiveness of the D-12 was similar to that of the dyspnoea domain of the CRDQ (effect size of 2.5).

This also is the first study to assess the responsiveness of the Arabic versions of the CRDQ and CAT as well as the first to report they are responsive to change following an AECOPD. These findings support the utilisation of the CRDQ and CAT in COPD population in the clinical and research settings in Saudi Arabia as well as in Arabic Gulf countries, as they were highly responsive questionnaires.

Further research with a larger sample of both genders from different regions in Saudi Arabia to investigate the measurement properties of the D-12 in the Arabic COPD population is required in order to increase its generalisability. Developing an interviewer-administrated version of the D-12 is recommended in order to increase the utilisation of the D-12 for those people with COPD who are not able to read or write. In addition, further studies are needed to evaluate the capacity of the D-12 to change in response to interventions such as pulmonary rehabilitation and oxygen therapy. Furthermore, further work is needed to determine the threshold for the minimal clinical important difference of the D-12.

6.2 Characteristics of those hospitalised with a severe AECOPD in Riyadh and the time course of their recovery

Although there was no specific research question around determining the characteristics of those hospitalised with a severe AECOPD in Riyadh, the data presented in Chapter 4 present novel information in this regard. Specifically, there no other studies have reported the length of stay or characteristics of people hospitalised for a severe AECOPD in Saudi Arabia. Data presented in Chapter 4 demonstrated that the people (of whom 25 males, 86%) who averaged 65 years of age and had a moderate severity had the median of six days for length of stay in hospital. This median of length of stay in hospital was consistent with that reported in 19 Australian people (of whom seven males, 37%) who averaged 70 years of age and had a moderate severity (length of stay was six days) (477). The results of this study demonstrated that the recovery of dyspnoea following a severe AECOPD can take up

to 70 days from hospitalisation. The prolonged recovery period presented in this study was consistent with earlier work (477). The findings are important for clinical practice as they will allow health professionals to provide Saudis who have been hospitalised with a severe AECOPD, and their families, information regarding the time course recovery.

Further work is required to determine the time course recovery of a mild to moderate AECOPD in Saudi with COPD for providing patients and their families information on the time course recovery for dyspnoea.

6.3 Physical activity and sedentary behaviour in Saudi nationals with COPD

The study presented in Chapter 5 is the first to provide a detailed description of the differences between males with COPD and healthy controls in Saudi Arabia in terms of time spent in walking based activity and sedentary behaviour, the duration of bouts spent in walking based activity and sedentary behaviour as well as peak stepping cadence. The study demonstrated that, compared with healthy controls, males with COPD spent 15 ± 12% less of their waking hours in walking based activity (defined as 1 ≥ steps/minute). In addition, when compared with healthy controls, males with COPD spent 15 ± 13% more of their waking hours in sedentary behaviour (defined as 0 steps/minutes). In keeping with these data was the finding that the proportion of males with COPD who accumulated ≥ 7,000 steps per day (the recommended amount of walking based activity to produce health benefits according to the guidelines of the American College of Sports Medicine (54)), was lower than that for healthy controls (7% versus 34%). These findings increase the importance of designing interventions aiming at increasing daily steps in males with COPD to meet the recommended amount of physical activity necessary to promote and maintain health.

When walking based activity was divided into intensity bands according to cadences described by the National Health and Nutrition Examination Survey (67), males with COPD spent less time in cadence bands equivalent to < 100 steps/min than healthy controls. However, there were no differences in high cadences ≥ 100 steps/min (a threshold equivalent moderate intensity physical activity) as neither group performed

any steps at these high cadences bands. These findings suggest that males with COPD as well as health controls are at greater risk of developing chronic diseases, such as cardiovascular and metabolic diseases, as they did not spend time participating in moderate intensity physical activity (54). Therefore, in Saudi Arabia, awareness of the health benefits of walking at moderate intensity needs to be promoted among the general public as well as males with COPD. However, the finding that both the peak and average 30-minute peak cadences were lower in males with COPD compared to that measured in the healthy controls suggests that males with COPD may have less capacity to walk at a moderate intensity.

Data presented in Chapter 5 also demonstrated that, compared with healthy controls, males with COPD, on average, accumulated walking based activity in shorter bouts and sedentary behaviour in longer bouts. These findings provide novel targets for patient education regarding participation in walking based activity and the way in which time is accumulated in sedentary behaviour. Specifically, data from this study suggest that males with COPD should be encouraged to accumulate time in walking in longer bouts and time in sedentary behaviour in shorter bouts for the purpose of health benefits such as reducing the risk of developing cardiovascular and metabolic disease (54, 61, 359). In addition, the

It is important to note that both Saudi males with COPD and healthy controls appeared to be physically less active than those from different countries such as Belgium and Brazil (56, 57). Reliance on cars instead of walking for short-distance travel, lack of quality physical education programs and facilities, poor air quality in many cities, and bad weather have been reported as the major barriers for Saudi males being physically active (73, 74, 474).

Studies that demonstrated changes in physical activity in people with COPD and other population have often used individual goal setting, collection of objective physical activity data in order to place goals and/or provide feedback, overcome barriers, encourage age adherence, motivational interviewing and regular contact with healthcare professionals to increase motivation (467-472). Therefore, these approaches need to be considered, in Saudi nationals, when implementing interventions to increase time of participation in physical activity and reduce time in sedentary behavior.

Data on physical activity and sedentary behaviour of Saudi females were not collected in this study. Several studies from different countries have reported that males were more physically active than females (447-451). Similar findings were also reported between males and females in Saudi Arabia (74, 453). However, those studies that quantified physical activity in the Saudi population used subjective methods (i.e. questionnaires). These methods have been reported to provide inaccurate information (361). Therefore, in Saudi Arabia, studies including large samples of both males and females with COPD and their healthy controls to measure physical activity and sedentary behavior, using objective measures, with consideration of sociocultural factors that limit their physical activity are required to understand the lifestyle adopted by the patients and healthy controls.

Finally, data presented in chapter 5 demonstrated moderate to strong associations between the components of D-12 and both time spent in walking based activity and sedentary behaviour. Of note, the associations between time in walking based activity and sedentary behaviour were stronger with the emotional response component of the D-12 ($r = \geq -0.63$ and $r = \geq 0.66$, respectively) than the quality component of the D-12 ($r = \geq -0.52$ and $r = \geq 0.46$, respectively). These findings indicate that males with COPD who experience a greater emotional response to dyspnoea than the quality of the sensation spend less time of waking hours in walking based activity and more time in sedentary behaviour. These findings suggest that interventions, such as cognitive behavioural therapy, which aim to minimise the emotional response to dyspnoea, may assist to increase the levels of physical activity and reduce sedentary behaviour in males COPD. However, the coefficient of determination for the association between emotional response to dyspnoea and time spent in walking based activity ($R^2 = 0.40$) or sedentary behaviour ($R^2 = 0.44$) demonstrates that, at most, only 44% of variance in either time spent in walking based activity or sedentary behaviour is explained by the emotional repose to dyspnoea. Therefore, this finding suggests that other important factors contribute to how males with COPD spent their daily time in walking based activity and sedentary behaviour such as lower exercise capacity, and a higher number of exacerbations in the past year (59).

The findings from this PhD study highlighted that further research is required to identify factors other than dyspnoea that contribute to the time spent in physical activity and sedentary behaviour by males with COPD, in Saudi Arabia. In addition, research is also needed to investigate if there are health benefits associated with the time spent in physical activity at different cadence bands by males with COPD as well as healthy males.

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APPENDICES

Appendix A: Dyspnoea- 12 questionnaire English version

Dyspnoea-12

This questionnaire is designed to help us learn more about how your breathing is troubling you.

Please read each item and then tick in the box that best matches your breathing these days.

If you do not experience an item tick the 'none' box. Please respond to all items.

Individual number: ..... **Date: ..... /..... /.....**

Item	None	Mild	Moderate	Severe
1. My breath does not go in all the way				
2. My breathing requires more work				
3. I feel short of breath				
4. I have difficulty catching my breath				
5. I cannot get enough air				
6. My breathing is uncomfortable				
7. My breathing is exhausting				
8. My breathing makes me feel depressed				
9. My breathing makes me feel miserable				
10. My breathing is distressing				
11. My breathing makes me agitated				
12. My breathing is irritating				

Appendix B: The back- translation version (first independent translator)

Dyspnoea-12

This questionnaire is designed to help us learn more about how your breathing is troubling you.

Please read each item and then tick in the box that best matches your breathing these days.

If you do not experience an item tick the 'none' box. Please respond to all items.

Individual number: ..... **Date: ..... /..... /.....**

Item	None	Mild	Moderate	Severe
1. My breath does not go in all the way				
2. My breathing needs more effort				
3. I feel short of breath				
4. I have difficulty catching my breath				
5. I cannot get enough air				
6. My breathing is uncomfortable				
7. My breathing is exhausting				
8. My breathing makes me feel depressed				
9. My breathing makes me feel miserable				
10. My breathing is distressing				
11. My breathing makes me agitated				
12. My breathing is irritating				

Appendix C: The back- translation version (second independent translator)

Dyspnoea-12

This questionnaire is designed to help us learn more about how your breathing is troubling you.

Please read each item and then tick in the box that best matches your breathing these days.

If you do not experience an item tick the 'none' box. Please respond to all items.

Individual number: ..... **Date: ..... /..... /.....**

Item	None	Mild	Moderate	Severe
1. My breath does not go in all the way				
2. My breathing requires more work				
3. I feel short of breath				
4. I have difficulty catching my breath				
5. I cannot get enough air				
6. My breathing is uncomfortable				
7. My breathing is exhausting				
8. My breathing makes me feel depressed				
9. My breathing makes me feel miserable				
10. My breathing is distressing				
11. My breathing makes me nervous				
12. My breathing is irritating				

Appendix D: The Arabic version of Dyspnoea-12 questionnaire

ضيق التنفس-١٢

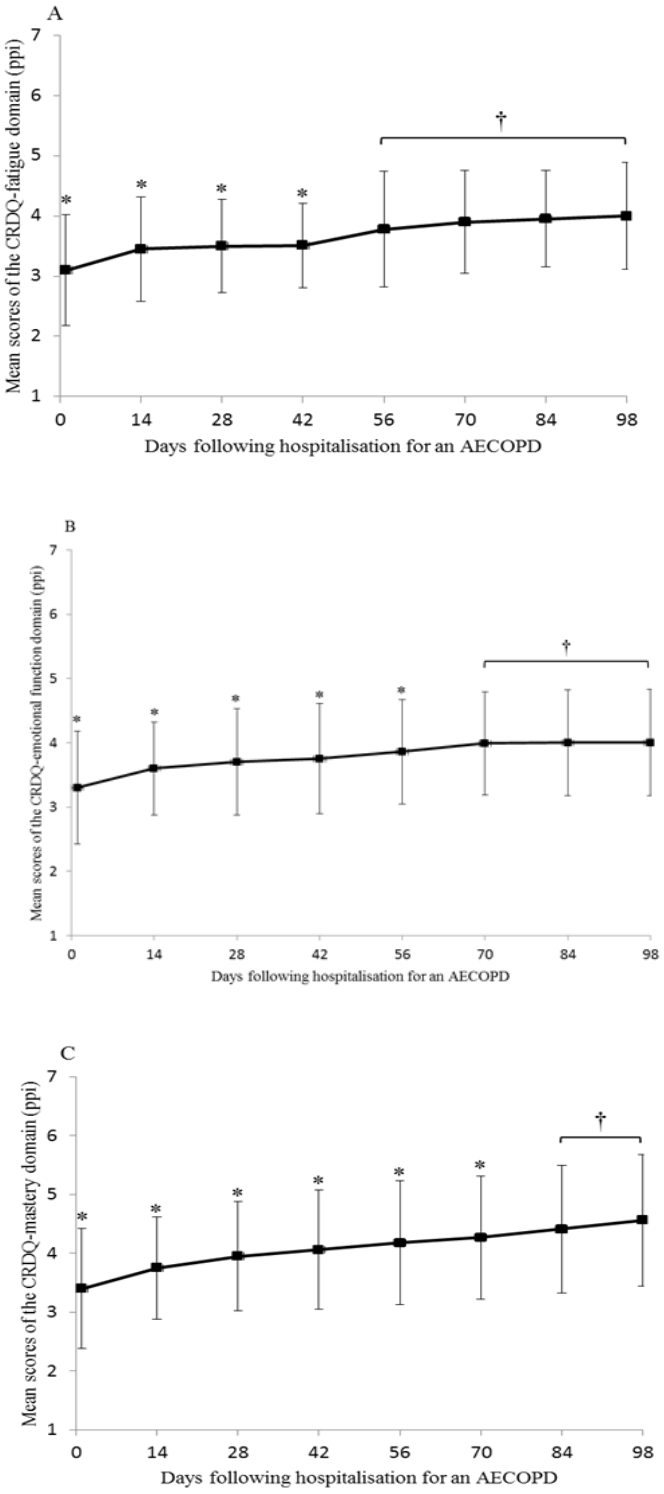
صمم هذا الاستبيان بهدف مساعدتنا على التعرف على مدى الإزعاج الذي يسببه لك ضيق التنفس

الرجاء قراءة كل فقرة و وضع علامة في المربع الذي يتناسب مع أفضل خيار فيما يتعلق بحالة تنفسك هذه الايام. إذا لم تكن تعاني من أحدى الحالات المذكورة أدناه ضع علامة في المربع (لايوجد). يرجى الاجابة على جميع الفقرات.

رقم الشخص:..... **التاريخ:.../.../...**

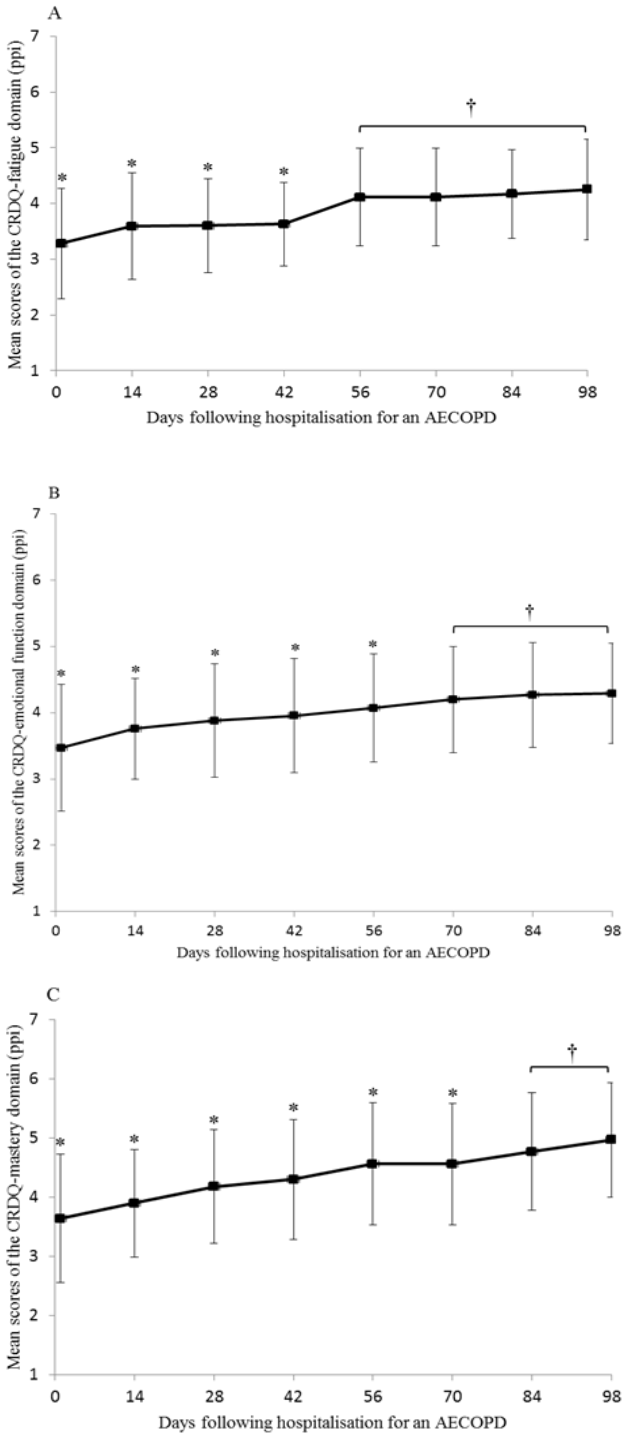
الفقرة	لا يوجد	خفيف	متوسط	شديد
١- لا استطيع اخذ النفس بصورة كاملة				
٢- تنفسي يتطلب مجهودا اكثر				
٣- أشعر بضيق في التنفس				
٤- اجد صعوبه في التقاط انفاسي				
٥- لا استطيع اخذ هواء كافي				
٦- تنفسي غير مُريح				
٧- تنفسي مُرهِق				
٨- تنفسي يجعلني اشعر بالإكتئاب				
٩- تنفسي يجعلني اشعر بالتعاسه				
١٠- تنفسي يضايقني				
١١- تنفسي يجعلني اشعر بالانفعال				
١٢- تنفسي مُزعِج				

Appendix E: The mean scores for domains of Chronic Respiratory Disease Questionnaire for all participants (n = 29)



Mean scores obtained for: A) fatigue, B) emotional function and C) mastery domains of the Chronic Respiratory Disease Questionnaire for all participants as one group. Data are mean and standard error. **Statistically significant difference* ($p < 0.05$) difference from the final administration (day 98). † No significant difference between consecutive administrations.

Appendix F: The mean scores for the domains of the Chronic Respiratory Disease Questionnaire for the participant who did not have re-exacerbations (n = 22)



Mean scores obtained for: A) fatigue, B) emotional function and C) mastery domains of the Chronic Respiratory Disease Questionnaire for The participant who did not have re-exacerbations. Data are mean and standard error. **Statistically significant difference* ($p < 0.05$) difference from the final administration (day 98). † No significant difference between consecutive administrations.