Respiratory function in people with Huntington's disease: Investigation and intervention

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Submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

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Abstract

Background

Huntington's disease (HD) is an inherited neurodegenerative condition characterised by progressive motor, cognitive and psychiatric symptoms. The most frequent cause of death is respiratory failure, yet little is known about respiratory function through the progression of the disease or the underlying causes of respiratory failure. A thorough exploration of the relevant literature led to the development of a conceptual framework for respiratory failure in people with HD. Within this framework respiratory failure was characterised as type 1 hypoxaemic and type2 hypercapnic failure and further evaluated through (i) an observational study to investigate respiratory function in people with HD, and (ii) the benefit and feasibility of inspiratory muscle training in people with HD. In order to develop understanding of potential underlying causes of type 1 hypoxaemic and type 2 hypercapnic respiratory failure, the observation study aimed to investigate if there was a difference in respiratory function between healthy controls and people with HD at different stages of the disease, and to explore factors that may influence or be influenced by respiratory function. The framework was further evaluated through the intervention study which investigated the feasibility and benefit of inspiratory muscle training in people with HD as a method of increasing capacity of the respiratory system.

Method

In the observation study 67 people with HD and 39 healthy control participants underwent a series of measurements of respiratory function based on underlying causes of type 1 hypoxaemic respiratory failure and type 2 hypercapnic respiratory failure. These included measurement of lung volume, respiratory muscle strength and endurance. Exercise capacity, physical activity, swallow and posture as potential influencing factors were also measured in people with HD.

In the intervention study 20 people with HD were randomly allocated either to inspiratory muscle training at 50% of maximal inspiratory pressure, or to training against a load suggested to have no effect, completed in the home. The training protocol was 30 breaths, twice daily for six weeks, which was preceded by a habituation period of one week. Sniff nasal inspiratory pressure, peak cough flow and 30 second sit to stand were measured before and after the intervention. The programme was supported by alternate weekly phone calls and home visits.

Results

All measures of respiratory function, except FEV_1/FVC were significantly decreased ($p < 0.001$) in people with manifest HD compared to healthy control participants and people with pre-manifest HD. There was no difference between healthy control participants and people with pre-manifest HD. Respiratory function demonstrated a significant linear decline with disease progression measured by the total functional capacity scale ($p<0.001$). In particular, peak cough flow was abnormal at the middle stage of the disease. Exercise capacity, physical activity, swallow and posture were significantly related to respiratory function in people with manifest HD (p range 0.016-0.001). In people with manifest HD, exercise capacity was 27.73% ±26.29 predicted and swallow capacity was abnormal in 84.80% of participants.
In the intervention study, five participants completed the intervention arm and 7 completed the sham arm. Adherence to the inspiratory muscle training programme ranged from 37-100% across both groups, with mean adherence rates of 70.67% ±26.35 and 74.53% ±21.03 for intervention and sham groups respectively. There was no difference in inspiratory muscle strength, peak cough flow or 30 second sit to stand as a result of the intervention. Participants and their carers identified carer support as a key enabler and life events as a barrier for carrying out the exercises.

Conclusion

The findings from this study indicate that people with HD are susceptible to type 1 hypoxaemic respiratory failure and predisposed to type 2 hypercapnic respiratory failure due to increased elastic and resistive loads and decreased capacity of respiratory muscles. The risk of type 1 hypoxaemic respiratory failure is high due to decreased swallow capacity and concomitant decreased cough efficacy. Decreased lung volume leading to hypoventilation may be impact on both type 1 hypoxaemic respiratory failure and lead on to type 2 hypercapnic respiratory failure. The predisposition to type 2 hypercapnic respiratory failure is due to decreased respiratory muscle capacity and increased elastic and resistive load. The study also highlighted the complex relationship between respiratory function, exercise capacity and physical activity. Although inspiratory muscle strength, cough efficacy and functional activity remained unchanged in this small sample, the results of the intervention study suggest that inspiratory muscle training is feasible in people with HD. Further studies should use protocols that are directly related to the primary outcome measure e.g. a power based protocol to improve cough efficacy or an endurance based protocol to improve physical activity.

A model of respiratory failure in people with HD incorporating both type 1 hypoxaemic and type 2 hypercapnic respiratory failure can be proposed based from the findings of the studies that informs future research and clinical management of people with HD.

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List of publications

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Table of abbreviations

ALS	Amyotrophic lateral sclerosis
ANOVA	Analysis of variance
BMI	Body mass index
CAG	Cytosine-adenine-guanine repeat
CI	Confidence interval
CV	Coefficient of variation
EMG	Electromyography
EMT	Expiratory muscle training
FEV_1	Forced expiratory volume in 1 second
FFM	Fat free mass
FRC	Functional residual capacity
FVC	Forced vital capacity
HD	Huntington's disease
ICC	Intraclass correlation coefficient
IMT	Inspiratory muscle training
IPAQ	International physical activity questionnaire
MEP	Maximal expiratory pressure
MET	Metabolic equivalent
MIP	Maximal inspiratory pressure
MND	Motor neurone disease
MVV	Maximal voluntary ventilation
MS	Multiple sclerosis
NIV	Non-invasive ventilation
P_aO_2	Partial pressure of oxygen in arterial blood
P_aCO_2	Partial pressure of carbon dioxide in arterial blood
PCF	Peak cough flow
PEFR	Peak expiratory flow rate
PEG	Percutaneous endoscopic gastrostomy
PD	Parkinson's disease
RV	Residual volume
SaO_2	Saturation of oxygen in arterial blood
SEM	Standard error of measurement
SNIP	Sniff nasal inspiratory pressure
TFC	Total functional capacity
TLC	Total lung capacity
TMS	Total motor score
UHDRS	Unified Huntington's disease rating scale
$\dot{V}O_{2max}$	Maximal oxygen consumption
6MWT	Six minute walk test

1 Introduction

1.1 Rationale for and development of the study

Huntington's disease is a genetic neurodegenerative condition affecting approximately 12/100,000 people in the United Kingdom (UK) (Evans et al. 2013). The genetic mutation results in death of cells and in particular medium spiny neurons within the striatum. Cell death in other areas of the brain results in a triad of motor, cognitive and behavioural problems (Ross and Tabrizi 2011). Symptoms become apparent in the middle stage of life, with death occurring 15-20 years from onset of symptoms (Bates 2005). This study originated from clinical observations that people with Huntington's disease (HD) die from respiratory problems, yet little empirical evidence existed in 2008 that quantified respiratory function or suggested that HD as a pathology could influence respiratory function. A study of 385 people with HD and 282 unaffected siblings from 1992 (Sorensen and Fenger 1992) had identified that pneumonia was the most common cause of death in people with HD, a later study in 2010 (Heemskerk and Roos 2010) further classified this as aspiration pneumonia. An abstract from 1985 (Leopold et al. 1985) reported observations of altered respiratory pattern in people with HD with more detail provided in an abstract that respiratory cycles in terms of tidal volume and respiratory flow were irregular and partial pressure of oxygen (P_aO_2) variable throughout the cycle (Fischer et al. 1983). It was concluded that this may be due to the underlying HD pathology or adaptation of the respiratory centre to maintain optimal oxygen tensions throughout the body. At the beginning of this study, little was known about pathological changes in the brainstem in people with HD and the influence this may have on respiratory control and function. A small study, n=12, exploring respiration during sleep found no difference in respiratory variability between people with HD and healthy controls (Bollen et al. 1988) yet a case study in a person with manifest HD and an altered sleep breathing pattern observed improvements in their breathing pattern following application of continuous positive airway pressure (Banno et al. 2005). In 2009, immunohistochemical staining of post-mortem HD brains identified for the first time that mutant Huntingtin was present in the brainstem (Herndon et al. 2009) which suggests that respiratory control may be influenced by HD pathology.

During the final writing up phase of this thesis, the first article describing respiratory function in people with HD was published (Reyes et al. 2014). This small study demonstrated that respiratory function was decreased in 18 people with manifest HD compared to 18 matched control participants and that the magnitude of decrease was associated with severity of motor symptoms. The study had high internal validity as demonstrated by reliability studies on

respiratory muscle strength and spirometric measurements, but lacked some external validity as smokers were excluded. The exclusion of people with late stage disease limited the range of motor symptoms and thus disease severity (mean Unified Huntington's Disease Rating Scale: Total Motor Score 40±15.7, range 13-62), and a lack of people with pre-manifest HD limited the conclusions that could be drawn from the findings. Outcome measures were limited as cough efficacy and inspiratory muscle strength measured nasally were not included. Declining respiratory function associated with worsening motor signs provided limited insight into the relationship between HD pathology and primary cause of death as outcome measures such as functional scores and other potential relational variables such as swallow, posture, exercise capacity and physical activity were not assessed.

Evidence from other neurodegenerative conditions e.g. Parkinson's disease (PD), multiple sclerosis (MS), motor neurone disease (MND)/amyotrophic lateral sclerosis (ALS) had identified respiratory dysfunction in relation to respiratory muscle strength (Buyse et al. 1997; Sathyaprabha et al. 2005; Sathyaprabha et al. 2009); lung volume (Sabate et al. 1996; Sathyaprabha et al. 2009) and upper airway obstruction (Buyse 2006).

The synthesis of this evidence highlights the importance of further investigation of respiratory function in people with HD and potential management strategies More specifically this led to the research question 'is respiratory function in people with HD different to that of healthy people?' with subsequent questions 'does respiratory function change over the progression of the disease?' and 'how could potential respiratory dysfunction be managed?'.

A thorough literature search enabled a conceptual framework of respiratory function in people with HD to be developed which could be evaluated using an iterative process of investigation. The literature search was limited to English language articles including human and animal studies, found using the following databases: Medline, EMBASE, AMED, and CINAHL from inception to July 2014. Key words and phrases were 'Huntington*' and 'striatum', 'cortex', 'brainstem', 'cerebellum', 'hypothalamus', 'respiratory centre', 'respiratory control', 'breathing', 'swallow', 'sleep', 'muscle', 'diaphragm', 'thorax', 'trunk', 'exercise', 'physical activity', 'physiotherapy'. For information related to respiratory failure search keywords were: 'respiratory failure', 'respiratory drive', 'breathing control', 'control', 'respiration', 'diaphragm', 'inspiratory muscles', 'expiratory muscles', 'lung compliance', 'elastic recoil'. For information related to respiratory function in people with neurodegenerative conditions the above search words were combined with: 'neuro*', 'huntington', 'multiple sclerosis', 'amyotrophic lateral sclerosis', 'motor neurone disease',

‘parkinsons’. For information related to outcome measures the following keywords were used: ‘swallow’, ‘posture’, ‘exercise tolerance’, ‘physical activity’ AND ‘measurement’, ‘reliability’, ‘validity’

An iterative investigative process enabled the development of studies that sit within the development phase of the Medical Research Council (MRC) framework for the development and evaluation of complex interventions. This phase encompasses identifying the evidence base, developing theory and modelling process and outcomes (Craig et al. 2008).

Little was known about respiratory function in people with HD or the impact of HD pathology on the respiratory system at the beginning of the study and the aims of this thesis were therefore to explore respiratory function in people with HD using a conceptual framework of respiratory failure and thereafter investigate whether inspiratory muscle training is feasible and can improve respiratory function in people with HD.

1.2 Structure of the thesis

The structure of this thesis is based on the development of ideas throughout the study period and the iterative investigative process. The study began by exploring how HD pathology may impact on respiratory function and respiratory failure with Chapters 2 and 3 exploring the literature in both these areas. The synthesis of evidence from these chapters was used to produce a conceptual framework of respiratory failure in people with HD which formed the basis of the observation study methodology in Chapter 4. The results of the observation study in Chapter 5, are discussed in relation to the conceptual framework in Chapter 6.

The intervention study was developed based on preliminary findings of the observation study and systematic review of physiotherapy strategies to manage respiratory problems in people with neurodegenerative conditions, see Chapter 7. The methods and results of the intervention study are described in Chapters 8 and 9 respectively with the findings discussed in Chapter 10. Conclusions from both studies along with limitations, clinical implications and recommendations for future research are provided in Chapter 11.

2 Huntington’s Disease

2.1 Introduction

Huntington's disease (HD) is an inherited neurodegenerative condition characterised by progressive motor, cognitive and psychiatric symptoms. Cognitive and/or personality changes often occur before the more noticeable motor signs of chorea and balance problems (Novak and Tabrizi 2010). George Huntington's original description of a condition that did not skip generations and resulted in 'nervous excitement' and 'tendency to insanity' (Bates 2005; Harper and Perutz 2001) is still as valid today as it was in 1872. The phenotypical expression of Huntington's disease has remained unchanged, but a greater understanding of the cause and progression of the disease has been gained through years of diligent research.
This chapter will review the literature regarding the pathological changes occurring in HD highlighting areas that may relate to respiratory function.

2.2 Genetics

HD is an autosomal dominant condition with children of an affected parent having a 50% chance of also being affected. The HD gene was mapped onto the short arm of chromosome 4 in 1983 (Bates 2005) and 10 years later in 1993, the HD gene was isolated and the mutation identified by the Huntington's Disease Collaborative Research Group (Huntington's Disease Collaborative Research Group. 1993). Pre-symptomatic testing for HD before the discovery of the gene in 1993 was based on the use of closely linked genetic markers involving family members, but the change to DNA testing enabled individuals to know whether they had inherited the mutation (Harper et al. 2000). The mutation is an expansion in the CAG (cytosine-adenine-guanine) portion of the chromosome and is measured in number of repeats of the protein with 0-35 repeats being normal, 36-40 incomplete penetrance with increased risk of developing the condition and more than 40 repeats being fully penetrant where the individual will most certainly develop HD (Bates 2005; Walker 2007). People with 36-39 CAG repeats may have variable age of onset and variable disease progression (Panegyres and Goh 2011). CAG repeats of over 28 are unstable during replication, particularly during spermatogenesis, resulting in children from male affected parents often having higher repeats than their parent. This is termed anticipation and explains the likelihood of inheritance of juvenile HD from fathers rather than mothers (Walker 2007). Juvenile HD is characterised by very early onset, younger than 21 years, with CAG repeats of over 70 (Bates 2005). The length of the CAG repeat influences the age of onset, individuals with longer repeats commonly have an earlier onset than those with shorter repeats (Tabrizi et al. 2009).

2.3 Epidemiology

People with the HD gene usually become symptomatic in the middle years of life, 40-50 years old (Kelly et al. 2009) with death occurring some 15-20 years after onset of symptoms (Bates 2005). Prevalence around the world is estimated to be 4-7/100,000 in Europe, 2.4-8.4/100,000 in Canada and 4.1-5.2/100,000 in the United States of America (Fisher and Semeka 2011), with a lower prevalence in Asia and Africa (Walker 2007). Evidence suggests a slightly higher frequency in Wales of 1 in 13,200, with concentrations within the Sirhowy and Afon Llywd valleys of Gwent (Harper 1986). The data were collected before genetic testing was available so the accuracy may be questionable; current prevalence data within Wales is not available. Recent data now show a prevalence of 12.3/100,000 [95% CI 11.2-13.5] in the United Kingdom (UK) with possible reasons for the increase given as more accurate diagnosis, more available therapies and a greater willingness to register HD as a diagnosis (Evans et al. 2013). This may still be an underestimation as secrecy and denial are still common in families with HD (Wexler 2010).

2.4 Assessment and measurement of Huntington's disease

Neuronal death due to mutant Huntingtin results in cognitive, motor, behavioural and functional dysfunction in people with HD which are typically assessed clinically using the Unified Huntington's Disease Rating Scale (UHDRS). The UHDRS was developed by the Huntington Study Group and originally assessed for reliability and consistency in 1996 (Huntington Study Group. 1996). The scale comprises 4 components i.e. motor, cognitive, behaviour and function (see Table 1 for details of the subsections within the scale).
People who are known to be gene positive for the HD gene usually have regular assessment using the UHDRS total motor score (UHDRS:TMS) which is used, in part, to categorise people into pre-manifest and manifest HD. The clinical diagnosis of manifest HD is based on the total motor score (UHDRS:TMS) and a diagnostic confidence level of 4 by the assessor. Diagnostic confidence is assessed as: 0 = normal (no abnormalities); 1 = non-specific motor abnormalities (less than 50% confidence); 2 = motor abnormalities that may be signs of HD (50-89% confidence); 3 = motor abnormalities that are likely signs of HD (90-98% confidence and 4 = motor abnormalities that are unequivocal signs of HD (≥ 99% confidence) (Huntington Study Group. 1999). The rate of decline in UHDRS has been assessed over a 36 month period with significant mean rate of change per year for: motor +4.748; cognitive -6.32 and TFC -0.44 (Meyer et al. 2012).

The diagnosis of manifest HD is based on unequivocal motor abnormalities in a subject at risk of HD (Huntington Study Group. 1999). Other conditions, from which a differential diagnosis is made include: dentatorubral-pallidoluysian atrophy; Huntington's disease-like 2; neurocanthocytosis and tardive dyskinesia. When the UHDRS has been completed, the examiner then decides with a confidence level of ≥ 99% whether the individual has manifest HD.

Table 1 The components of the Unified Huntington's Disease Rating Scale

Motor 0 - 124 Higher scores represent decreased motor ability	**Cognitive 0 - >300** Lower scores represent decreased cognitive ability	**Behavioural 0 – 93** Higher scores represent poorer behavioural function	**Functional 0 – 13** Lower scores represent decreased functional ability
Oculor motor function	Verbal fluency	Mood	Functional assessment
Dysarthria and tongue protrusion	Symbol digit modalities test	Behaviour	Independence scale
Chorea	Stroop interference	Psychosis	Total functional capacity score
Dystonia		Obsessiveness	
Gait			
Bradykinesia			
Postural stability			
Finger tapping			
Luria test			

When HD is clinically diagnosed as manifest, the progression of the disease is categorised using the total functional capacity score, see Table 2 (Shoulson and Fahn 1979). The typical categorisation is:

- early: TFC 11-13;
- middle: TFC 3-10;
- late: TFC < 3

(European Huntington's Disease Network Physiotherapy Working Group. 2009).

Table 2 Total Functional Capacity (Shoulson and Fahn 1979)

Category of TFC				
Occupation	**Finances**	**Domestic Chores**	**Activities of Daily Living**	**Care Level**
Normal 3	Normal 3	Normal 2	Normal 3	Home 2
Reduced capacity for normal job 2	Slight assistance 2	Impaired 1	Minimal impairment 2	Home with chronic care 1
Marginal work only 1	Major assistance 1	Unable 0	Gross tasks only 1	Full time skilled nursing 0
Unable 0	Unable 0	Unable 0	Total care 0	Full time skilled nursing 0

2.5 Pathology of Huntington's disease

The HD gene is responsible for the production of a protein called Huntingtin which is found throughout the human body, particularly in the central nervous system and peripheral tissue. Mutation of the gene causes Huntingtin to be an expanded protein that aggregates or clumps within cell nuclei (Bates 2005), neuronal dendrites and synapses (Bano et al. 2011) and cytoplasm (Ross and Tabrizi 2011). Both the aggregated and soluble form of mutant Huntingtin is thought to disrupt functioning of transcription, cellular trafficking and mitochondria within cells. Mitochondrial dysfunction is thought to lead to altered calcium metabolism, increased production of reactive oxygen compounds and increased sensitivity to apoptosis (Costa and Scorrano 2012). This dysfunction eventually leads to cell death which occurs most frequently within the striatum and the cerebral cortex with phenotypical expression being observed as movement disorders, cognitive and behavioural dysfunction. This loss of physiological function may also be accompanied by a gain in toxic function of mutant Huntingtin (Ross and Tabrizi 2011), but symptoms do not arise until later in life due to protective cellular molecular networks (Finkbeiner 2011). The medium spiny neurons within the striatum may be particularly susceptible to mitochondrial dysfunction with the high energy demands of these neurons leading to their subsequent death (Costa and Scorrano 2012).

2.5.1 Striatal and cortical dysfunction in Huntington's disease

Neuronal cell death leads to loss of volume in the brain and this has been observed in people who are pre-manifest as well as those with manifest disease. A prospective, multinational

observation study (TRACK-HD, n= 366 at baseline; 332 (91%) at 24 month follow up) (Tabrizi et al. 2012) reported that people with pre-manifest HD close to onset of symptoms and people with early stage HD demonstrated greater annual decreases in whole brain volume compared to control subjects, the predominance of this atrophy being within the striatum. This loss of both white and grey cells was correlated with measures of function (TFC) and motor scores of the UHDRS. The total motor score includes measures of chorea, bradykinesia and dystonia which may occur throughout the progression of the disease and may be explained by dysfunction of cortico-striatal neuronal activity through neuronal loss.

The striatum receives input from a wide range of cortical areas; in relation to motor activity these areas include the supplementary motor area, arcuate pre-motor area, motor cortex and somatosensory cortex (O'Callaghan et al. 2014). The putamen in the dorsolateral region of the striatum receives information relating to sensorimotor function and output is primarily divided into the direct and indirect pathways returning to the cortex. The direct pathway projects to the substantia nigra pars reticulate and the internal portion of the globus pallidus whilst the indirect pathway projects to the external portion of globus pallidus before following the direct pathway (Galvan et al. 2012). The indirect medium spiny neurones appear to be more susceptible to cell death than the direct neurones, with post mortem animal and human studies showing decreased indirect pathway neurones in people with pre-manifest, early stage and people with fully symptomatic HD and sparing of the direct pathway in the early stages of the disease (Galvan et al. 2012). The loss of indirect projections from the striatum results in decreased inhibition of the thalamo-cortical pathways and involuntary movement such as chorea. Appropriate voluntary movements continue as the direct pathway remains functional (Fenney et al. 2008). Through the progression of the disease, choreiform movements spread from distal to proximal muscles, including the trunk and face (Roos 2010).

Choreic buco-lingual movements influence swallow ability and abnormal swallow has been identified in people with HD which is characterised by swallow incoordination, repetitive swallows and inability to stop respiration during swallow (Kagel and Leopold 1992). Choking, coughing and aspiration during the pharyngeal phase of swallowing and shortened oral transit time are consequences of swallow incoordination (Heemskerk and Roos 2011). Normal swallow is both a reflex and planned manoeuvre involving not only the swallow mechanism but also pulmonary function and situational factors. Abnormal tongue movements associated with choreic buco-lingual movements may impact on the oral phase of swallow. Inability to protrude the tongue is one of the classical signs of HD and correlates with disease

burden and progression scores (Reilmann et al. 2010) and basal ganglia volume (Tabrizi et al. 2009). It is difficult to assert the exact causes of impaired tongue protrusion but central sensorimotor feedback and integration circuits are likely to be involved (Reilmann 2013). Swallow can be affected by cortical, cranial and brainstem pathology (Hughes 2003) but as yet, the specific underlying reasons for abnormal swallow in people with HD is unknown. Appropriate integration between breathing and swallow (see section 3.3.1) and situational factors such as food preparation, appropriate posture as well as adequate protective mechanisms are necessary for safe and effective oral feeding (Hughes 2012; Hughes and Wiles 2000).

Although no empirical evidence reports choreic movements of the diaphragm, clinical observations have observed altered breathing patterns (Leopold et al. 1985). This alteration in breathing pattern may be due to other causes e.g. disruption in the generation of breathing pattern from the brainstem (see section 3.3.1). Dystonia is highly prevalent in people with HD and can be distinguished from chorea in that the former is sustained muscle contraction producing twisting or repetitive movements and abnormal postures whereas choreic movements are random and flowing (Louis et al. 1999). Dystonia is involuntary and recent evidence from post mortem brains of 37 people with HD suggests that loss of interneurons within the striatum may explain the imbalance of muscle contraction, although loss of neurons within the direct pathway may also explain these gross movements (Reiner et al. 2013). Patterns of trunk flexion and upper limb sustained shoulder internal rotation with elbow extension (Louis et al. 1999) may impact on normal functioning of the rib cage influencing the biomechanics of breathing (see section 3.3.2.3).

As HD progresses medium spiny neurons of the direct pathway are lost, as well as cortical neurons, with losses in the primary and pre-motor areas correlating positively with motor dysfunction (Estrada Sánchez et al. 2008). In late stage HD 95% of striatal and 30% of cortical neurons may be lost (Estrada Sánchez et al. 2008) resulting in voluntary movement dysfunction. This may be observed as akinesia and/or bradykinesia, although this slowing of movement can be observed early in the condition and also alongside chorea (Fenney et al. 2008). A small study identified the co-existence of non-smooth trajectory and slowing of movement which was different to healthy control subjects during a reach to eat task (Klein et al. 2011). This study also identified that proximal movements, including the trunk, compensated for distal movement impairment, but as the disease progressed poor posture i.e. slumping, resulted in poor sitting balance. The functional consequences of bradykinesia and akinesia are postural instability, impaired gait and falls. Postural instability is common in

people with HD (Brozova et al. 2011), with control of the centre of gravity compromised during functional tasks such as sit to stand (Panzera et al. 2011). Walking speed is decreased in both people with pre-manifest HD (Rao et al. 2008) and manifest HD (Bilney et al. 2005) with 75-80% of people with HD reporting falling more than once in the previous year (Busse et al. 2009; Grimbergen et al. 2008).

Postural instability of the trunk and slumping posture may influence the synchrony between abdominal muscles and respiratory muscles in postural control; the shape of the thoracic cage and inspiratory capacity and the position of the diaphragm within the thoracic cavity and subsequent force generation (see section 3.3.2). If bradykinesia is a common finding of voluntary movement, this may have implications during voluntary breathing activities such as singing and also activities that require adaptation of automatic respiration e.g. coughing; swallowing and speech (see section 3.3.1).

Voluntary movements rather than involuntary movements have been reported to correlate with cognitive impairment, specifically short term memory and executive function in a small study of 45 people with HD across the stages of the disease (Klempíř et al. 2009). The relationship between cognitive impairment and motor impairment was further analysed in a large cohort study of 1882 people with HD which found that those with chorea had better global and cognitive function than those with hypokinetic-rigid HD irrespective of age and disease duration (Hart et al. 2013). These findings highlight the complexity of the cortico-striatal loops that influence cognition and behaviour as well as sensori-motor functioning. The caudate has connections with the frontal and parietal association cortices and the nucleus accumbens has connections with limbic structures such as the amygdala and hippocampus (O'Callaghan et al. 2014); disruption of these extensive interconnections possibly explaining the cognitive and behavioural symptoms in people with HD. A large study of 516 people with pre manifest HD demonstrated that motor functions were associated with specific volumes of putamen (speeded tapping), caudate (UHDRS total motor score), globus pallidus (bradykinesia and chorea) and nucleus accumbens (oculomotor), and also that putamen volumes were associated with cognitive measures that included a motor component, whereas caudate volumes were associated with cognitive tasks that emphasised executive control rather than motor control. There were no relationships between psychiatric measure and striatal volumes or between cortical grey matter volumes and motor, cognitive, psychiatric or functional variables identified. This may have been due to the sample not exhibiting

psychiatric symptoms and degree of cortical loss during the pre-manifest phase of the disease (Aylward et al. 2013).

Cognitive changes are often the first noticeable signs in people with HD (Kingma et al. 2008). A lack of ability to shift strategies for tasks, deficiencies in motor and procedural learning and loss of executive function is seen in people with pre-manifest HD with attention, acquisition of motor skills, planning and executive functions progressively declining in people with manifest HD. Dementia gradually develops in the late stage of the disease with slowing of information processing, depression and apathy (Giralt et al. 2012). In people with pre-manifest HD, motor planning and sensory perceptual processing are the best indicators of time to diagnosis, after controlling for CAG repeat, age and motor impairment (Harrington et al. 2012). Memory loss is also noted in the early stages of the disease (Paulsen et al. 2008). Motor planning deficit is therefore not confounded by motor symptoms but is most likely due to cortico-striatal dysfunction (Giralt et al. 2012; Harrington et al. 2012). Other suggested causes for cognitive dysfunction are hippocampal and/or synaptic dysfunction (Giralt et al. 2012) and metabolic alterations in the posterior cingulate cortex (Unschuld et al. 2012). Psychiatric disturbances such as irritability, aggressiveness, depression and obsessive compulsive behaviour are also features of the disease (Estrada Sánchez et al. 2008; van Duijn et al. 2014), with apathy being a predominant feature in advanced stages of the disease (van Duijn et al. 2014). The ability to perform activities of daily living is influenced by both cognitive (Peavy et al. 2010) and behavioural (Hamilton et al. 2003) deficits with Hamilton et al. (2003) suggesting that profound apathy, lack of initiative and irritability may interfere with functional activities, even if the necessary motor and cognitive capacity is retained.

2.5.2 Other brain areas affected by Huntington's disease

The striatum and cortex have been the main focus of central nervous system research in people with Huntington's disease, based on the clinical features of motor, cognitive and behavioural impairment. As Huntingtin is a ubiquitous protein, the effects of mutant Huntingtin could potentially be found in all parts of the brain and indeed all tissues of the body. In relation to movement dysfunction, a small study of eight post-mortem brains of people with HD showed atrophy of the cerebellum with neuronal death in the deep nuclei. This loss could influence the quality of limb, trunk and eye movements as well as the maintenance of posture and balance (Rub et al. 2013). In relation to cognitive and behavioural impairments, a narrative review of human and animal studies identifies pathological changes in the hypothalamic and limbic systems. Changes include loss of grey

matter and volume as well as blood and cerebrospinal fluid biochemical changes. Clinical features associated with these changes include depression, anxiety, body weight changes, circadian rhythm changes and sleep disturbances (Petersen and Gabery 2012). Sleep disturbance is thought to be common amongst people with HD with a small qualitative study demonstrating 77% of people had abnormal sleep, which was confirmed by sleeping partners (Videnovic et al. 2009). Animal studies have also shown disrupted sleep even in the pre-manifest stage of the disease (Kantor et al. 2013). It is still unclear, however, whether sleep and circadian rhythms disruption in people with HD are due to the underlying disease pathology or whether they are secondary to the consequences e.g. sleep deprivation, of having a neurodegenerative condition (Morton 2013).

Emerging from a number of sleep studies is some evidence of sleep related breathing disorders which may exist in people with later stage disease. Studies assessing apnoea-hypopnea events showed no difference between people with early and mid-stage disease and healthy controls (Arnulf et al. 2008; Cuturic et al. 2009; Wiegand et al. 1991) yet in more advanced stages of the disease, three of 13 cases demonstrated abnormal patterns (Antczak et al. 2013). These are all relatively small studies and the lack of control participants in Antczak et al limits the external validity of the findings. A case study describing snoring and an apnoea – hypopnea index of 6.6 events per sleeping hour in a woman with HD demonstrated that management using continuous positive airways pressure abolished nocturnal respiratory systems. The sleep related breathing problems described may result from altered circadian rhythms due to hypothalamic pathological changes or represent changes in respiratory rhythm generation within the brainstem. Mutant Huntingtin has been identified in the brainstem with degeneration of pontine nuclei within post mortem studies of people with HD (Herndon et al. 2009; Rub et al. 2014) and magnetic resonance imaging showing progressive atrophy of the brainstem alongside that of the cortex and striatum in people with early HD (Hobbs et al. 2010). These findings may have implications for the generation and control of respiration in people with HD (see section 3.3.1).

2.5.3 Huntington's disease outside the central nervous system

Research over the last decade has begun to examine non central nervous systems of the body in order to understand the potential influence of mutant Huntingtin in other tissues and systems such as skeletal muscle and the cardiovascular system.

Skeletal muscle atrophy is a recognised observation in people with HD (Sassone et al. 2009) although the pathological mechanisms underlying this atrophy are unclear. Mutant Huntingtin

has been found in muscle cells in the R6/2 mouse (Orth et al. 2003) with some evidence, yet not conclusive, of myopathic changes in people with HD (Sassone et al. 2009). The relationship between mutant Huntingtin and atrophy may be due to mitochondrial dysfunction in skeletal muscle as suggested in an in vitro study in human subjects with HD (Ciammola et al. 2011). Skeletal muscle atrophy in animal studies may be due to a complex interaction between increased protein synthesis within the muscle which creates an energy deficit due to decreased mitochondrial energy production (She et al. 2011). Changes in skeletal muscle fibres have also been documented; Ribchester et al. (2004) noted a reduction in mouse muscle fibre diameter and Strand et al. (2005) demonstrated a progressive loss in fast twitch fibres with concomitant gain in slow twitch fibres in both mouse models and humans. Mitochondrial dysfunction is thought to lead to a reduction in muscle bulk and reflected functionally in a low anaerobic threshold (Ciammola et al. 2011). Force generation in muscles in people with HD may also be influenced by emerging evidence of altered membrane potential and hyperexcitability (Waters et al. 2013), though this relationship is as yet not fully established. Clinical evidence supports these pathological findings, with Busse et al. (2008a) identifying peripheral muscle weakness in people with HD. Whether this weakness is reversible remains unknown, with findings demonstrating no change in lower limb strength after strengthening exercises (Khalil 2012) and a single case study demonstrating strength gains following a progressive strengthening programme (Meaney et al. 2008). Functional gains, however, were observed by Khalil (2012), similar to positive findings after intensive general rehabilitation, including specific strengthening exercises (Zinzi et al. 2007). Physiological changes therefore exist in skeletal muscle in people with HD, but the relationship between muscle strength and function remain unclear. It is also unknown if the physiological changes seen in peripheral skeletal muscle are also evident within the diaphragm and other muscles of respiration. If changes in muscle fibre type from fast to slow fibre type do occur, these could lead to a decrease in explosive muscle function such as during coughing whilst changes in energy metabolism may influence respiratory muscle endurance (see section 3.3.2).

Respiratory muscle function is also influenced by nutrition (see 3.3.2), with atrophy a potential consequence of the weight loss observed in people with HD. Unintended weight loss has been observed throughout the disease progression of HD, including the pre-manifest stage (Aziz and Roos 2013) with the first systematic evidence being provided by Farrer and Meaney (1985). This anthropometric study investigated thirty three variables to look for differences between affected, ‘at risk’ and control groups. The ‘at risk’ group included family

members who had no symptoms of the disease and this method of categorisation was used prior to DNA testing. Results indicated that people with HD differed from controls in all body weight parameters including body mass index (BMI) as measured by kg/m^2. BMI, all skinfold measurements and upper arm, chest and abdominal circumferences were all reduced in people with HD. When factor analysis was carried out on the data the primary factor that accounted for the overall variance was BMI (42.6%).

More recent work, which included genetic testing, explored this further. Marder et al (2009) examined calorie intake, dietary composition and BMI in participants who were at risk for HD, but had not had genetic testing prior to the study. Participants who had CAG $\geq$ 37, but not diagnosed as HD, had a significantly lower BMI than those with CAG $\leq$ 37, 27.0Kg/m^2 ±5.4 and 28.4 kg/m^2 ±6.6 respectively, with calorie intake rather than BMI being significantly correlated with CAG repeat. BMI in people with HD has been found to be significantly less than healthy controls with values ranging from 22.2Kg/m^2 ± 2.4 to 25.9Kg/m^2 and 24.6Kg/m^2 ±1.5 to 27.68Kg/m^2 ±0.16 respectively (Djousse et al. 2002; Trejo et al. 2004) with a rate of decline of -0.15Kg/m^2 per year (Aziz et al. 2008). Although weight loss has been suggested as a prominent sign in people with HD, the participants in the studies noted were not actually underweight when compared to the World Health Organisation BMI classifications (World Health Organisation. 2006), of normal (18.50-24.99) and pre-obese (25.00-29.99).

Weight loss, as identified by decreased BMI, may be due to chorea, dysphagia, malabsorption or increased metabolism (Marder et al. 2009; van der Burg et al. 2008; van der Burg et al. 2011). The relationship between chorea and decreased BMI is unclear, as BMI is decreased in people with HD who have minimal chorea (Djousse et al. 2002) but cannot be excluded as some relationship does exist between the two variables (Marder et al. 2009). Marder et al (2009) also noted that although BMI was reduced, calorie intake was increased, which may be due to a gastrointestinal problem, confirmed in animal but not human studies (van der Burg et al. 2011). Animal models also describe increased metabolism as the most likely cause of weight loss in HD mice (van der Burg et al. 2008) with similar findings emerging in human studies (Krzysztoń-Russjan et al. 2013).

Peripheral muscle weakness and respiratory muscle dysfunction may also impact on exercise tolerance and the potential to undertake physical activity (see section 3.3.4). Self-reported physical activity as measured by the International Physical Activity Questionnaire is low to moderate in people with HD (Quinn et al. 2013). More specifically, daily step count in people with HD who fall (3853 ±1796) is significantly less than those who do not fall (6729 ±1494)

(Busse et al. 2009); the step count being classified as ‘sedentary’ for fallers and ‘low active’ for non-fallers (Tudor-Locke and Bassett Jr 2004). Developing a progressive exercise program is a key theme of physiotherapy intervention (Busse et al. 2008b; European Huntington's Disease Network Physiotherapy Working Group. 2009), with emerging positive evidence of the feasibility of an exercise intervention directing further research (Busse et al. 2013). This is a complex area, with evidence that having a lifestyle that includes physical activity does not influence age of onset of symptoms, yet following a passive lifestyle e.g. listening to music, watching television, leads to earlier age of onset of symptoms (Trembath et al. 2010). Additionally, physical activity is associated with higher lung functional values whilst a sedentary lifestyle is associated with lower values in the general population (Jakes et al. 2002), which impacts on cardiovascular respiratory function and, potentially, exercise capacity.

Reduced physical activity in people with HD can lead to lack of participation in an individual’s normal lifestyle and may compromise physical and psychosocial well-being (Helder et al. 2001). Whether as a consequence or a cause of decreased physical activity, evidence exists to indicate that people with manifest HD have a reduced work capacity, low anaerobic threshold and early increase in blood lactate which are thought to reflect abnormal oxidative metabolism in skeletal muscle (Ciammola et al. 2011). This translates into decreased exercise capacity which appears to occur in people with HD (Quinn et al. 2013), with people with manifest HD walking 381.66m ±129.97 and people with pre-manifest HD walking 515.75m ±101.66 in the six minute walk test, although predicted values were not reported. Decreased exercise tolerance and potential decreased activity in people with HD is likely to be due to a number of factors. Neural dysfunction can lead to postural instability and falls; abnormal energy systems within skeletal muscle can lead to reduced work capacity and the combination of these factors may lead to decreased activity and deconditioning.

Ability to exercise and be physically active may also be influenced by autonomic dysfunction in people with HD affecting the cardiovascular system. Autonomic nervous system dysfunction has been identified in people with early to middle stage HD (Andrich et al. 2002) as well as people with pre-manifest HD (Aziz et al. 2010). Both sympathetic and parasympathetic systems are affected and with disease progression, sympathetic activity predominates resulting in reduced modulation of cardiovagal activity (Andrich et al. 2002). There is a high incidence of cardiac failure in people with HD, although the exact underlying mechanisms are unknown with many factors such as central control, autonomic control and

potential relationships between psychiatric and cardiac symptoms needing further investigation (Abildtrup and Shattock 2013).

2.5.4 Huntington's disease and respiratory function

The review of HD pathology highlights a number of aspects that may influence respiratory function in people with HD. Respiratory muscle strength in people with HD may be influenced by central factors e.g. disturbance in central respiratory control as a consequence of mutant Huntingtin within the brainstem (Herndon et al. 2009), or as a consequence of muscle atrophy (Sassone et al. 2009). Endurance may be affected less than strength as a gain in slow twitch fibres and decrease in fast twitch fibres has been noted in animal and human studies in HD (Strand et al. 2005). The rigidity and bradykinesia noted in later stage HD (Andre et al. 201; Han et al. 2010) may also impact on respiratory muscle activity resulting in a potential decrease in respiratory muscle strength. Rigidity of chest wall muscles may reduce chest wall compliance through associated stiffening of tendons and ligaments and ankylosis of costosternal and thoracovertebral joints (Buyse 2006). Postural instability (Brožová et al. 2011) may also impact on the biomechanical actions of the diaphragm with resultant decreased force production. Decreased respiratory muscle force generation will lead to decreased capacity of the respiratory muscle pump and with alterations in posture may lead to decreased lung volume, increasing the load on the respiratory pump. This load may also be increased through disruption of airflow from the lungs as a consequence of laryngeal and pharyngeal dysfunction identified in swallow studies (Heemskerk and Roos 2011).

The most frequent cause of death in people with HD is aspiration pneumonia (Heemskerk and Roos 2010; Sorensen and Fenger 1992), but at the onset of this study little was known about respiratory function throughout the progression of the disease. Aspiration pneumonia could be a singular event due to swallow difficulties and although the underlying cause of swallow dysfunction is unknown in people with HD, it is a common clinical occurrence (Heemskerk and Roos 2011; Kagel and Leopold 1992). The inhaled liquid and/or solid would precipitate an inflammatory response and clinical signs of pneumonia such as high temperature and cough would be present. If secretions cannot be cleared through effective cough, gaseous exchange will be impaired and death due to hypoxaemia occurs. Aspirations of small amounts of solid and/or fluid may go unnoticed, but if they occur repeatedly, chronic damage to the respiratory epithelium will ensue (Wallis and Ryan 2012). The long term effects of repeated micro-aspirations and consequent epithelial damage may influence respiratory function and gradually lead to respiratory failure that is both hypoxaemic and hypercapnic.

These different types of respiratory failure are termed type 1 hypoxaemic respiratory failure and type 2 hypercapnic respiratory failure. Type 2 hypercapnic respiratory failure may be the consequence of altered central drive, decreased respiratory muscle capacity as well as an increase in load placed upon the respiratory system.

The physiological and pathologic changes associated with type 1 hypoxaemic and type 2 hypercapnic respiratory failure will be discussed in relation to HD pathology and other neurodegenerative conditions in the following chapter in order to develop a framework for the observation study of respiratory function in people with HD.

3 Respiratory failure

3.1 Introduction

The preceding chapter reviewed the pathological changes of Huntington's disease with specific reference to aspects that may impact on respiratory function. Cortico-striatal dysfunction leading to chorea, dystonia and bradykinesia may impact on respiratory muscle movement and the consequences of alterations in trunk posture and postural instability may influence the biomechanics of respiratory muscle force generation and the synchrony of postural and respiratory muscle activation. Loss of neurons within the brainstem may influence the generation and control of respiratory rhythm, whilst skeletal muscle changes and weight loss may reduce capacity of the respiratory muscles. This chapter will explore the underlying causes of type 1 and type 2 respiratory failure in order to identify the key areas for assessment in the observation study of respiratory function in people with HD. The categorisation of respiratory failure as described by Hart (2008) was used as a framework for the review of the literature as it deconstructed type 1 and type 2 respiratory failure into components that could relate to the underlying pathology of HD and the clinical signs and symptoms of respiratory failure. As little was known about respiratory function in people with HD, evidence from other neurodegenerative conditions was used to potentially validate the Hart framework for people with neurodegenerative conditions. Parkinson's disease (PD), multiple sclerosis (MS) and motor neurone disease (MND)/amyotrophic lateral sclerosis (ALS) were chosen as comparable conditions as their pathologies include the central nervous system and clinical symptoms show some similarity to HD.

Hart (2008) categorises respiratory failure into lung failure leading to type 1 hypoxaemic respiratory failure and pump failure leading to type 2 hypercapnic respiratory and acknowledges that both can occur concurrently in the same person. Lung failure causing hypoxaemia can be the result of pathological mechanisms such as mismatch of ventilation and perfusion; impaired diffusion across the respiratory membrane; low partial pressure of inspired oxygen; alveolar hypoventilation and a shunting of de-oxygenated blood past non-ventilating portions of the lung. Pump failure results from an imbalance between neural respiratory drive, the load placed upon the respiratory muscles and the capacity of the respiratory muscles. This framework will be used alongside evidence of respiratory function in people with PD, MS, MND/ALS to develop a conceptual framework for respiratory failure in people with HD. The framework will therefore provide the basis for the investigation of respiratory function in people with HD.

3.2 Type 1 hypoxaemic respiratory failure

Type 1 hypoxaemic respiratory failure is due to lung tissue failure i.e. a failure of gaseous exchange as a consequence of hypoventilation with consequent ventilation perfusion mismatch; low partial pressure of inspired oxygen and/or impaired diffusion. As decreased partial pressure of inspired oxygen is only likely to occur with decreased atmospheric oxygen e.g. at altitude (Peacock 1998) and impaired diffusion usually due to pulmonary oedema (West 2008a) and respiratory pathology such as emphysema (Hari and Mackenzie 2007), the physiological mechanisms of ventilation will be explored in order to identify potential dysfunction in people with HD.

The primary role of the respiratory system is exchange of carbon dioxide (CO_2) and oxygen (O_2) to and from the external environment respectively. This is achieved through an efficient bidirectional flow of approximately six litres of air per minute through a highly branched conducting system and gaseous exchange via specialist alveolar type 1 epithelial cells (Rackley and Stripp 2012). As the system is open to the environment specialist cells provide protection from potential antigens. The large conducting airways are lined with ciliated, mucous secretory, neuroendocrine and basal cells (Green et al. 2012) which provide a mechanical removal of particles absorbed in a viscous layer of mucous through movement of the cilia (Rackley and Stripp 2012). Alveoli are lined with alveolar type 1 epithelial cells, alveolar type 2 cells and alveolar macrophages. Alveolar type 2 cells produce surfactant which lowers the surface tension within the alveolus (Rackley and Stripp 2012) whilst macrophages within the alveolus and those found in the airway epithelium are involved in defence through the inflammatory system (Hussell and Bell 2014). A breach in the defence mechanism of the airways and alveoli will prevent adequate gaseous exchange and can lead to type 1 hypoxaemic respiratory failure. In relation to HD pathology, little is known about changes in epithelial tissue although animal studies have shown decreased mucosal thickness in the gastrointestinal tract in mice (van der Burg et al. 2011). Further research is needed to investigate whether these changes also occur in the respiratory tract and whether this influences gaseous exchange.

Alveolar hypoventilation and subsequent decreased gaseous exchange may be a consequence of atelectasis and/or pneumonia. Atelectasis can be caused by airway obstruction, compression of the airway and/or an increase in surface tension within the airway (Peroni and Boner 2000). Airway closure occurs during tidal breathing when the closing volume exceeds end expiratory lung volume; closing volume increasing in conditions

such as chronic obstructive pulmonary disease (COPD) and asthma; end expiratory lung volume decreasing with obesity and heart failure (Milic-Emili et al. 2007). Airway closure occurs in small airways as residual volume is approached during expiration due to surface tension instability within the airways and collapse of airway walls (Bian et al. 2010; Heil et al. 2008). Repeated closure and re-opening of airways during tidal breathing causes sheer stresses within the airways leading to cell injury (Bian et al. 2010) and consequent peripheral airway pathological changes. Alteration in the liquid film coating the airways will influence surface tension compounding airway closure and also reduce protection against infection (Heil et al 2008). The postural changes caused by dystonia (Louis et al. 1999) and decreased physical activity (Quinn et al. 2013) may reduce tidal and total lung volumes in people with HD leading to airway closure and atelectasis. Atelectasis results in alveolar hypoventilation with consequent hypoxaemia via ventilation perfusion mismatch and may cause predisposition to respiratory infection. Type 1 hypoxaemic respiratory failure with atelectasis as an underlying cause represents a gradual increase in alveolar hypoventilation which may be overlaid by a respiratory infection causing gaseous exchange to be inadequate.

Pneumonia as a common respiratory infection leads to hypoxaemia, with aspiration pneumonia accounting for 5-15% of all cases (Lanspa et al. 2013) and is the leading cause of death in people with Parkinson's disease (Williams-Gray et al. 2013); multiple sclerosis (Lalmohamed et al. 2012); Huntington's disease (Heemskerk and Roos 2010) and motor neurone disease (Rafiq et al. 2012). Aspiration is a consequence of ineffective swallow which is evident in people with HD (Kagel and Leopold 1992), PD (Johnston et al. 1995) and MS (Calcagno et al. 2002) which is compounded by evidence of ineffective cough in people with PD (Ebihara et al. 2003) and MS (Aiello et al. 2008). Pneumonia may be a consequence of aspiration of oropharyngeal contents or of liquids and/or solids. Large volume aspirations as defined by >0.8mL/Kg in children are associated with rapid and acute hypoxaemia, whilst microaspirations or silent aspirations, that can occur without notice, can result in chronic damage to the epithelium (Wallis and Ryan 2012). Susceptibility to pneumonia is increased through smoking by facilitation of adherence of bacteria to the lower airway epithelium whilst inhibiting the normal production of antimicrobial and antiviral agents and impairing mucociliary clearance (Feldman and Anderson 2013). Rates of smoking also appear to be higher in people with HD (49%) compared to the United States of America national average of 28.4% (Byars et al. 2012) making them more susceptible to pneumonia.

The likelihood of type 1 hypoxaemic respiratory failure appears to be high in people with HD as aspiration pneumonia is the most common cause of death ((Heemskerk and Roos 2010). Hypoxaemia may be an acute event from a large aspiration or may be due to escalating alveolar hypoventilation and microaspirations. The following section reviews the assessment of type 1 hypoxaemic respiratory failure and also cough efficacy as this is a key factor in the removal of secretions.

3.2.1 Measurement related to type 1 respiratory failure

Clinical diagnosis of type 1 hypoxaemic respiratory failure is through analysis of arterial blood partial pressures (P_a) of oxygen (O_2) with a value of < 8KPa being indicative of hypoxaemic failure. An alternative to invasive blood gas analysis is the measurement of saturation of oxygen (S_aO_2) using pulse oximetry. Although this provides an accurate representation of arterial blood gas (Decker et al. 1989) it is susceptible to light and movement artefacts (Tremper 1989).

Effectiveness of swallow as a precursor to aspiration and cough as an airway clearance technique may also be measured objectively. Assessment of swallow is discussed in section 3.3.4. Bach and Saporito (1996) identified that a peak cough flow (PCF) rate of 160L/min was necessary for successful extubation of people with neuromuscular ventilatory impairment and this value has become the benchmark measurement for effective cough particularly in people with neuromuscular weakness (Bott et al. 2009). Bott et al. (2009) also recommend that if PCF < 270L/min and the person is unwell, interventional strategies to increase PCF should be employed. PCF is a measure of volitional cough effectiveness whereas reflex cough sensitivity and intensity can be measured by inhalation of stimulants (Morice et al. 2007). In people with dysphagia however, measurement of reflex cough is not recommended due to lack of adequate evidence (Hammond and Goldstein 2006).

3.3 Type 2 hypercapnic respiratory failure

Type 1 hypoxaemic respiratory failure is primarily due inadequate gaseous exchange at alveolar level. Type 2 hypercapnic respiratory failure however may have complex underlying impairment of central respiratory drive and/or capacity of the respiratory muscles and/or increased load on the respiratory system. Although Hart (2008) draws clear distinctions between the two types of failure, progressive atelectasis as a cause of alveolar hypoventilation and hypoxaemia, may increase the load on the respiratory system and the development of pump failure. Type 2 hypercapnic respiratory failure is defined clinically as a

$P_aO_2 \leq 8$KPa concurrent with a P_aCO_2 of $\geq$ 6PKa and is characterised by difficulty sleeping, sleepiness during the day and morning headache due to nocturnal desaturation (Polkey et al. 1999). The three components underlying type 2 respiratory failure i.e. central drive; capacity and load are explored in more detail in the following sections in order to identify potential dysfunction in people with HD.

3.3.1 Central respiratory drive

The brainstem is a distinctive part of the central nervous system and includes the centres of origin and/or termination of the cranial nerves (except the olfactory cranial nerve); the reticular formation and numerous relay nuclei (Nieuwenhuys 2011). The reticular formation is a network of polysynaptic interconnections responsible for the generation of a number of patterned activities. These activities include eye movements, chewing, walking, respiration, coughing, cardiovascular activity, sleeping and arousal (FitzGerald et al. 2012). The respiratory central pattern generator within the brainstem is responsible for the homeostatic maintenance of carbon dioxide and oxygen in relation to the demands of the body at an automatic or basic level of functioning (Bianchi and Gestreau 2009). The respiratory muscles must also adapt to other functions such as speech, swallow and posture in both voluntary and involuntary (automatic) contexts (Aleksandrova and Breslav 2009). The following sections will review the generation of both automatic and voluntary breathing as well as the adaptation of breathing to non-respiratory events. As mutant Huntingtin has been identified within the brainstem in people with HD (Herndon et al. 2009; Rub et al. 2014) with associated atrophy (Hobbs et al. 2010), there is a potential for the disruption of generation and control of respiration from the brainstem. Cortico-striatal dysfunction in people with HD may also impact on voluntary breathing activities.

3.3.1.1 Automatic respiratory rhythm

Automatic respiratory rhythm is generated in the pontomedullary region of the brainstem from which, predominantly bilateral, bulbospinal connections are made with anterior horn cells in the spinal cord (Hudson et al. 2011; Koritnik et al. 2009). Other categories of respiratory neurons that exist are propriobulbar which provide an inter-neural brainstem network and laryngeal motoneurons which connect with the vagus (laryngeal) nerve (Bianchi and Gestreau 2009). The basic rhythm of breathing is generated by the pre-Botzinger complex (inspiratory) and the retrotrapezoid nucleus (expiratory). The pre-Botzinger complex sends projections to the diaphragm and external intercostal muscles to drive the inspiratory pump muscles; while the retrotrapezoid nucleus stimulates the abdominal muscles and

internal intercostals; both groups activating the laryngeal and tongue muscles which act as valves to modulate airflow resistance (Feldman et al. 2013). The central pattern generator of respiratory rhythm can be broken down into three phases: inspiration; post inspiration/early expiration and late expiratory. These phases are integrated with activity of nerves controlling the valve muscles, with the vagus and recurrent laryngeal nerves activating abduction of the glottis in inspiration and adduction during expiration. Other neuronal integration occurs with the glossopharyngeal nerve responsible for pharyngeal dilation during inspiration; the pharyngeal branch of the vagus nerve responsible for pharyngeal constriction in expiration and the hypoglossal nerve producing tongue protrusion during inspiration (Bianchi and Gestreau 2009). Modulation with cranial nerves including that of the hypoglossal nucleus controlling tongue protrusion helps maintain a clear airway (Sawczuk and Mosier 2001). It appears that the genioglossus is stimulated with respiratory manoeuvres, but that voluntary tongue protrusion can occur without respiratory muscle involvement (Wang et al. 2007).
The basic rhythm of respiration is modulated by both central pontine and peripheral pulmonary feedback loops which control the length of inspiration and expiration as well as frequency of breathing (Molkov et al. 2013). The pons receives afferent input from the hypothalamus, cortex amygdala, periaqueductal grey matter and pulmonary mechanoreceptors, whilst the medulla receives afferent information from the central and peripheral chemoreceptors, mechanoreceptors and cardiovascular afferents (Nogues and Benarroch 2008). Within the mid brain, therefore, the central pattern generator creates the basic inspiratory and expiratory drive which is then modulated by inputs from higher centres and sensory afferents in order to maintain homeostasis of arterial oxygen and carbon dioxide levels.
The complexity of neural circuitry involved in automatic breathing may be affected by pathological changes in HD with evidence of widespread white and grey matter throughout the cortex, striatum and brainstem (Hobbs et al. 2009; Tabrizi et al. 2012). Evidence of breathing control dysfunction in people with HD is limited, with one abstract describing abnormal breathing pattern (Leopold et al. 1985), and another abstract further defining this as variable tidal volume, flow and timing (Fischer et al.1983). Although it is not known whether central generation of respiratory rhythm is affected in HD, there is a likelihood that dysfunction cortico-striatal neuronal loops could influence the pattern generated. The pattern may lose its smooth transition from inspiration and/or demonstrate incoordinated muscle contraction. Brainstem dysfunction is also noted by the inability of people with HD to protrude their tongue (Reilmann et al. 2010).

Evidence in people with PD also suggests that their respiratory control is compromised. In a small study of 19 people with mild to moderate PD an abnormal ventilatory response to hypercapnia and abnormal occlusion pressure response in was found in 47% and 73% of the subjects respectively, yet all subjects maintained normal respiratory flow and volumes (Seccombe et al. 2011). These results may indicate brainstem involvement in the early stages of PD.

3.3.1.2 Adaptation to non-respiratory events

The respiratory rhythm adapts and contributes to non-respiratory functions such as coughing, swallowing and vomiting (Bianchi and Gestreau 2009) and speech (Aleksandrova and Breslav 2009). There is thus integrated control of both 'valve' muscles i.e. those that control the upper airway and 'pump' muscles that act on the chest wall (Butler 2007). Breathing and swallowing are highly co-ordinated activities, controlled by neural interactions within the brainstem with connections to the cranial nerves. It is proposed that swallow, breathing and coughing share elements of neural control, and that the swallow mechanism reconfigures the respiratory neural network in order to protect the airways (Davenport et al. 2011). Factors such as P_aO_2 that influence breathing also influence swallowing, with pharyngeal dysfunction in turn impacting on breathing (Hårdemark Cedborg et al. 2009). Control of the tongue is also thought to be integrated with the central pattern generators for swallow and breathing in order to allow the safe movement of food to the oesophagus (Sawczuk and Mosier 2001). The predominant pattern of breathing during swallow is inspiration-expiration-swallow-apnoea-expiration. Swallow apnoea is thought to be an active process, with the diaphragm being active throughout pharyngeal swallow representing central control which aims to ensure that breathing has stopped before a bolus enters the pharynx. Approximately 200ml of tidal volume is held during and is expired after swallow (Hårdemark Cedborg et al. 2009). Sensory information from the oral cavity is co-ordinated with the activity of the cranial nerves responsible for swallow and results in a safe passage of food to the oesophagus (Hughes and Ackermann 2003). These integrated mechanisms ensure safe passage of food and fluid and reduce the likelihood of aspiration.

The components of swallow dysfunction identified in people with HD are not just those related to choreic buco-lingual movements; the inability to stop respiration during swallow and short oral transit time (Heemskerk and Roos 2011; Kagel and Leopold 1992) may indicate a central processing dysfunction in adaption to non-respiratory events. The presence of mutant Huntingtin within the pons and medulla (Herndon et al. 2009) would suggest that

neural dysfunction may occur within the brainstem which may help to explain the existence of abnormal swallow-breathing co-ordination in people with HD. The close proximity of the hypoglossal nerve (cranial XII), and the respiratory nuclei in the brainstem in conjunction with integration of genioglossal, swallow and breathing function suggest that central control of breathing may be impaired in people with HD.

Abnormalities have also been identified in swallow patterns of people with PD. Videofluoroscopy assessment during the swallowing of a liquid bolus identified a predominantly normal swallow pattern of expiration following swallow apnoea, but participants who had decreased swallow safety were more likely to inspire and have a shorter swallow apnoea phase (Troche et al. 2011). These studies highlight the need not only for further exploration of brainstem function in neurodegenerative conditions but also the need for clinical assessment and management of swallow function in order to prevent aspiration.

3.3.1.3 Voluntary respiration

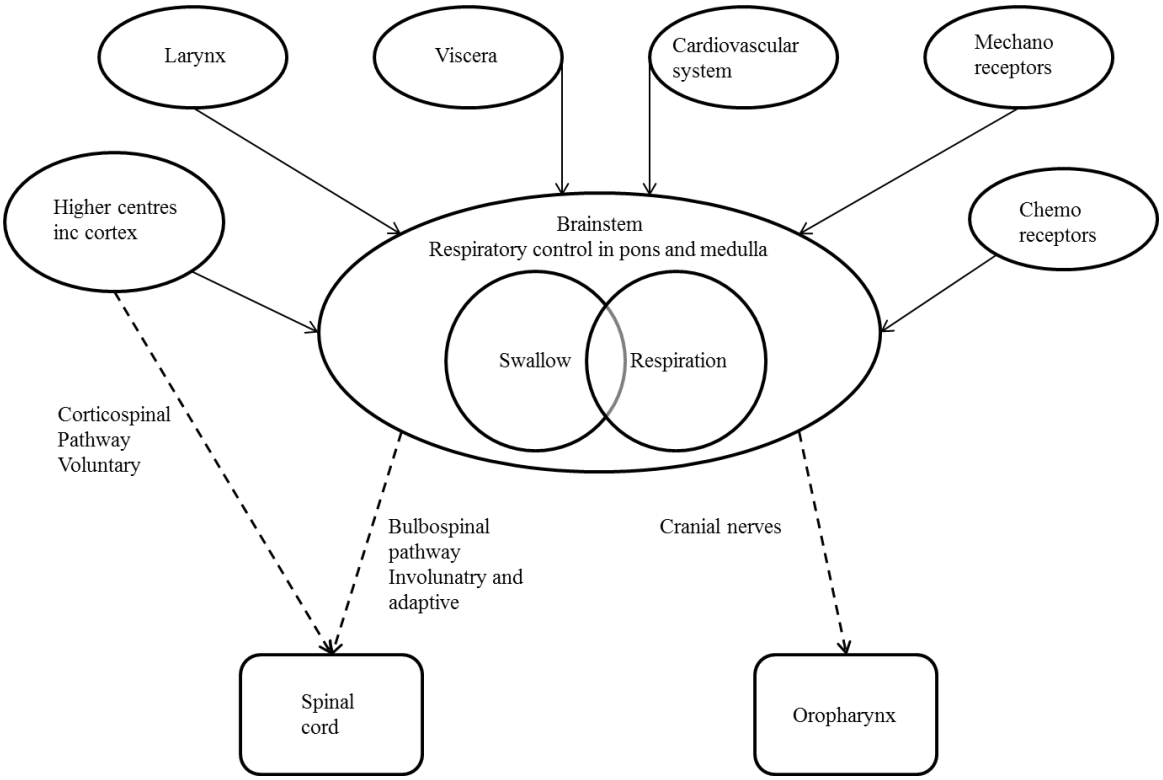
The rhythmic involuntary control of breathing can be altered for activities such as singing, playing musical instruments or carrying out breathing exercises. Voluntary control of respiratory muscles could be compared to that of other skeletal muscle, with cortico-spinal pathways from the primary sensorimotor cortex, lateral premotor cortex supplementary motor area and cingulated motor area to the spinal cord via the internal capsule and brainstem (FitzGerald et al. 2012). There is evidence that this pathway does exist for some fibres (Corfield et al. 1998; Urban et al. 2002) but that other fibres may also integrate with automatic respiratory control before descending to the spinal cord (Butler 2007; Hudson et al. 2011). Although unsubstantiated by evidence, it is thought that voluntary and involuntary breathing have a high level of co-operation in order to fulfil the roles and demands placed upon the respiratory system (Haouzi 2011). Small studies of transcranial magnetic stimulation in people post cerebrovascular accident (CVA) demonstrated that inspiratory muscle activity (Urban et al. 2002) and expiratory muscle strength (Harraf et al. 2008) were reduced when the affected hemisphere was stimulated. Muscle activity and strength were not reduced when the participants were stimulated at spinal level providing evidence that respiratory muscles are under some cortico – spinal control.

Abnormal cortio-striatal circuitry in people with HD results in bradykinesia in peripheral skeletal muscles during voluntary movements, but it is unknown whether this could influence voluntary control of respiratory muscles during activities such as singing or whether it may influence the ability to carry out breathing exercises.

3.3.1.4 Input to central respiratory drive

As well as input from the cortex, the brainstem receives input from other higher centres such as the hypothalamus and amygdala. The amygdala as part of the limbic system is primarily associated with the emotion of fear and via multi-synaptic pathways leads to hyperventilation (FitzGerald et al. 2012). The lateral hypothalamus controls functional activities such as food intake, locomotion, sleep and wakefulness alongside breathing. Hydrogen ion concentration and partial pressure of carbon dioxide are detected by chemoreceptors which project to the medulla (Burdakov et al. 2013). This central chemoreceptor system is essential for acid-base homeostasis throughout the body and is assisted by peripheral chemoreceptors in the carotid and aortic bodies. Arterial hypoxaemia is detected by the peripheral chemoreceptors with altered input to the brainstem when PaO_2 falls below 8kPa (Calverley 2005), which provides a rapid response in acute situations. Other receptors which feed information into the central respiratory centre are mechanoreceptors within the lung, joints, peripheral muscle and larynx. Lung receptors included pulmonary stretch receptors in airway smooth muscle, irritant receptors between airway epithelial cells, J receptors in the alveolar walls and bronchial C fibres in the bronchial circulation. Mechanoreceptors in joints and muscle are thought to be the stimulus to ventilation during exercise. Muscle spindles within the diaphragm control the strength of contraction especially when load is increased (West 2008b). Input from irritant receptors in the larynx is thought to stimulate the ventral and dorsal respiratory groups to produce the specific breathing pattern necessary for cough (Shannon et al. 1996). Figure 1 provides a simplified diagram illustrating the integration that occurs in the central drive to respiration, based on Bianchi and Gestreau 2009, Butler 2007, Feldman et al 2013, Haouzi 2011, Hudson et al 2011, Nogues and Benarroch 2008, Sawczk and Mosier 2001, Shannon et al 1996.

Figure 1 Central drive to respiration



Key

Input ——→

Output – – – – →

3.3.1.5 Measurement of respiratory drive

As ventilation is controlled by both voluntary and automatic pathways, it is impossible to completely separate their contributions. Voluntary control through the cortico-spinal pathways may be assessed by breath holding time; the length of time someone can hold their breath reflects both the activity of respiratory reflexes and the ability to voluntarily control diaphragmatic contractions (Shneerson 1988). Breath holding time reflects not only cortico-spinal control, but the patency of feedback systems such as chemoreceptors, proprioceptors in the respiratory muscles and the perception of effort. The break in breath holding is usually an involuntary breath, suggesting that rhythm generation in the brainstem over-rides voluntary control. Normal values for this measurement are unclear due to different study methods e.g. preceding lung volume (Parkes 2006). The intensity of respiratory drive can be assessed by measuring the pressure generated when the airway is briefly occluded within the first 0.1 second of inspiration. This method is thought to reduce other influences such as the Hering-

Breuer reflex as it is a transient measure. The measure however is dependent upon the strength of the respiratory muscles and the mechanics of the chest wall (Shneerson 1988). Further analysis of breathing pattern and lung volumes can be achieved through plethysmography which has advantages over spirometry in that residual volume, functional residual capacity and inspiratory and expiratory reserve volumes can be determined. (Criee et al. 2011). Analysis of flow time or flow volume spirograms can provide visual and quantitative measures of breathing pattern (Williams et al 2014). Although used predominantly in people with obstructive respiratory disorders, they could be used to explore respiratory patterns in people with neurodegenerative conditions.

Visual analysis of breathing pattern at rest may be observed by the anteroposterior and lateral movement of the rib cage due to action of scalene and diaphragm respectively; inward and outward movement of abdomen due to displacement of abdominal viscera (Banner 1995); a ratio of inspiratory to expiratory of approximately 1:2 (Molkov et al. 2013) with little activation of accessory respiratory muscles (Banner 1995). Technological advancement has seen the introduction of respiratory inductive plethysmography, which uses two inductance sensors usually placed around the chest and abdominal walls, that detect changes in cross sectional area. This method has the advantage of being non-invasive and relatively portable allowing it to be used in a range of situations e.g. critical care people with sleep related disorders and in clinical research (Brullman et al. 2010).

3.3.2 Capacity of the respiratory system

Information integrated within the central nervous system drives the respiratory pump to achieve the goal of optimal gaseous exchange. This relies on the capacity of the peripheral nervous system to relay the information and for the respiratory muscles to work appropriate force. This section will explore transmission of central drive; biomechanical and physiological aspects of respiratory muscles and respiratory muscle dysfunction in people with neurodegenerative conditions.

3.3.2.1 Transmission of central drive

The centrally generated pattern of breathing is transmitted via respiratory motor neurons in the spinal cord to the respiratory muscles. Specifically, the diaphragm is innervated by the phrenic nerve C3-5; the intercostals by their adjacent thoracic nerves (Gatzoulis 2008); scalene by the cervical nerve C3-8 and sternocleidomastoid by the cervical nerve C2-3 (Standring 2008). The abdominal muscles: rectus abdominus; internal and external oblique and transverse abdominus are used during expiration and are supplied by: T6-7; T6-12; T6-12

and L1 respectively (Borley and Healy 2008). Any pathology that interrupts transmission of the respiratory impulses may lead to respiratory failure. Conditions likely to cause respiratory failure by this means are spinal cord lesions above C3, amyotrophic lateral sclerosis (ALS), Guillain-Barré syndrome and critical illness neuromuscular abnormalities (Hart 2008). It is unknown whether peripheral nerve transmission is influenced by HD pathology.

3.3.2.2 Assessment of nerve transmission

Nerve conduction to the respiratory muscles can be assessed in one of two ways: electromyography and stimulation. As the control of respiration is complex, so are its measurements, as both of these tests are inter-related and also relates to the biomechanics of the respiratory muscles.

Electromyography (EMG) is used to assess the level and pattern of nerve impulses to the muscle via electrodes; the signal being amplified and filtered before visual analysis. Electrodes may be surface, intramuscular or oesophageal. Surface electrodes are placed over or as close to the muscle being assessed which relies on the assessor's anatomical knowledge. Currently there are no standards for placement of the electrodes which may influence reliability, but the advantage of surface electrodes is that they are simple to use and non-invasive. Disadvantages include cross talk from other muscles and influence of subcutaneous fat or chest wall deformity (American Thoracic Society/European Respiratory Society. 2002). These disadvantages are reduced if intramuscular electrodes are used although this method does carry a small risk of pneumothorax (Saadeh et al. 1993). Direct measurement of diaphragm electrical activity may be gained by oesophageal electrodes which are mounted on a catheter and inserted via the mouth or nose. The electrode is then positioned at the level of the crural diaphragm. This method may produce reliable outcomes, but can be unpleasant for the subject and carries risk of regurgitation and aspiration (Duiverman et al. 2004).

Whilst EMG measures spontaneous electrical activity, the efficiency of neural and neuromuscular transmission may be assessed by actively stimulating peripheral nerves, spinal nerves or the cerebral cortex. Stimulation may be via implanted electrodes and external electrical or magnetic fields. Following stimulation of the phrenic nerve, EMG activity of the diaphragm is measured; from this the nerve/diaphragm latency can be measured as well as the compound muscle action potential. Cortical stimulation is a highly specialised skill and although not always selective can measure the central conduction time for the diaphragm (American Thoracic Society/European Respiratory Society. 2002).

3.3.2.3 Biomechanics of respiratory muscles

The respiratory muscles may be divided into inspiratory and expiratory muscles although each group influences the other. Inspiratory muscles include the diaphragm, scalene, sternocleidomastoid, external intercostals and parasternal muscles and their action is to increase the vertical, transverse and antero-posterior dimensions of the chest (Gatzoulis 2008). The diaphragm, as the main muscle of respiration, is thin and musculotendinous with muscle fibres radiating from a central tendon to three lumbar vertebral bodies, the posterior of the xiphoid process and the inner surfaces of the lower six ribs creating the lumbar, sternal and costal diaphragm segments respectively (Ratnovsky et al. 2008). This domed shape means that, unlike most skeletal muscles that exert forces along their axis, the diaphragm acts to balance a pressure load perpendicular to the axis of the muscle (Wilson and De Troyer 2010). Contraction of the diaphragm expands the pleural cavity in proportion to the extent of the descent of the diaphragm displacing the abdominal contents until the limit of extensibility of the abdominal wall is reached (Wilson and De Troyer 2010). At this point the central tendon then becomes a fixed point from which the muscle fibres of the diaphragm contract, elevating the second to tenth ribs and moving them outward to increase the transverse dimension of the thorax. This movement, particularly in the seventh to tenth ribs, is often termed the 'bucket handle movement' and occurs due to the vertical arrangement of the lumbar and costal segments of the diaphragm (Gatzoulis 2008). The alignment of the vertical fibres in close proximity to the inner surface of the ribs is called the zone of apposition, these fibres are relatively thicker than in the dome suggesting that this zone has primary responsibility for creation of respiratory pressure (Wait and Johnson 1997). The multi-dimensional action of the diaphragm has led to it being described as a piston in an expanding cylinder (Gauthier et al. 1994).

The force generated by the diaphragm depends on lung volume as this influences both the length of the muscle and its radius of curvature. The surface area of the diaphragm decreases linearly as lung volume increases from residual volume to total lung capacity (Gauthier et al. 1994), resulting in lower pressure generation (De Troyer and Wilson 2009). Conversely, when end expiratory lung volume is decreased as in exercise, the diaphragm is stretched and is working at its optimal length tension relationship. This balance is delicate as in high intensity exercise with increased lung volumes, the diaphragm becomes shorter and less effective (Romer and Polkey 2008).

The anterior dimension of the thorax is increased through a 'pump handle action': the sternum and first two ribs being raised by contraction of the scalene muscles with further

elevation of the rib cage due to contraction of the external intercostals (Ratnovsky et al. 2008). Sternocleidomastoid is usually inactive during quiet breathing, but, as the major accessory inspiratory muscles, become active during high levels of ventilation increasing 'pump handle movement' (Banner 1995). The primary role of the intercostal muscles is to stiffen the rib cage preventing an inward movement due to the decrease in pressure in the thorax (Gatzoulis 2008; Lumb 2010).

Normal quiet expiration is a passive event caused by the elastic recoil of the lung tissue, inspiratory muscles and rib cage (Feldman et al. 2013). Inward elastic recoil of the lung tissue is due to surface tension acting on the air/water interface lining the alveoli. Recoil due to elastin and collagen fibres does however occur if the lungs are nearly fully extended. Surface tension within the alveoli is dependent upon the radius of the alveoli and the liquid lining. Forces within the alveoli are less than expected due to the presence of surfactant, which is a protein containing fatty acids that are hydrophobic at one end and hydrophilic at the other end. Surfactant lowers the surface tension and serves to protect alveoli from collapsing at low lung volumes (Van Golde et al. 1988). This has been discussed in terms of atelectasis and subsequent hypoventilation in relation to type 1 hypoxaemic respiratory failure (see section 3.2). Active expiration occurs when there is an increased load placed upon the respiratory system. This can occur due to exercise, pathology or activities such as sneezing or coughing. The ribs will be actively lowered by the internal intercostals and contraction of the abdominal muscles pulls the abdominal wall inward, pushing the diaphragm cranially. Abdominal muscles involved in active expiration are rectus abdominus, external oblique, internal oblique and transverse abdominus (Ratnovsky et al. 2008). With the diaphragm in a more domed position, the fibres are lengthened enabling it to contract more forcefully in the subsequent inspiratory contraction (Romer and Polkey 2008).

The diaphragm is continuous with transverse abdominus, forming an uninterrupted structure with lumbar fascia and the rectus sheath surrounding the abdominal cavity (Downey 2011). Interaction between the inspiratory muscles and the abdominal muscles involved in expiration is thought to occur throughout the respiratory cycle with abdominal muscle activity during late inspiration and extending through expiration into the following inspiration (Iizuka 2011). Expiratory activity in late inspiration increases in hypercapnic conditions with the potential to increase expiratory flow (Abe et al. 1996) and therefore maintain CO_2 homeostasis. Lung inflation and deflation can be finely controlled by this dual control system as well as expiratory muscle activity providing mechanical stability to the respiratory system (Iizuka 2011).

Synchrony between respiratory and abdominal muscles does not only influence ventilation; respiratory muscles are also involved in postural control (Bianchi and Gestreau 2009). The diaphragm acts as an anticipatory stabiliser during upper limb movements with the intercostal and parasternal muscles involved in trunk rotation (Hudson et al. 2011) with the relationship between postural control and respiration being adaptable dependent upon the body's movement and needs (Massery et al. 2013). The integration of respiratory and postural muscles is highlighted in two small studies in healthy subjects demonstrating diaphragm recruitment during sit ups and weightlifting exercises (power lift, bench press and biceps curl) (Al-Bilbeisi and McCool 2000) and strengthening of the diaphragm following a progressive strengthening programme of biceps and sit up exercises (DePalo et al. 2004). In healthy people, the postural role of the diaphragm during arm movements is reduced when respiratory demand increases suggesting compromise of trunk stability due to preferential respiratory function over postural actions (Hodges et al. 2001). Experimental mechanically and chemically induced hyperventilation in healthy subjects has also shown that disturbance of respiratory pattern reduced postural stability (David et al. 2012) which has implications for people with respiratory disease in terms of their postural stability and potential consequences for activity limitation.

Decreased postural stability has been observed in people with COPD compared to healthy control subjects and in particular those with decreased inspiratory muscle strength. Functionally this was related to an increase in reliance on ankle rather than back muscle proprioceptive mechanisms which may increase the risk of falls in people with COPD (Janssens et al 2013). Differences in diaphragm activity during upper and lower limb activity have also been observed in people with low back pain. Magnetic resonance imaging of the diaphragm showed that people with low back pain had smaller excursions of the anterior and middle portions of the diaphragm during resistance of upper and lower limb activity compared to healthy subjects (Kolar et al. 2012). These studies do not reflect cause and effect but rather the complex integration of roles of both respiratory and postural muscles.

Additionally, postural control is also influenced by the opening and closing of the glottis which influences both thoracic stability and balance mechanisms (Massery et al. 2013). During a tip toe movement designed to alter posture healthy subjects inhaled during the upward movement, held their breath when whole body balance was required and exhaled during the downward movement. The breath hold was attributed to the maintenance of spinal stability by increasing intra-abdominal pressure (Lamberg and Hagins 2013). For people with

neurodegenerative conditions, the co-existence of swallow dysfunction and postural instability may influence or be influenced by respiratory muscle weakness.

Co-ordination of muscle control is important in the gross movements required for inspiration and expiration, adaptation of ventilation in response to physiological changes and stability of the trunk during movements. Dystonic postures in people with HD and in particular trunk flexion, may cause the diaphragm to become more domed and beyond its optimal length for force generation. The zone of apposition may also be influenced by a flexed posture with potential reduction of bucket handle movement and reduced ventilation in lower lung zones. Dystonic patterns in the upper limb may disturb the synchronicity between respiratory, upper limb and trunk postural muscles resulting in impoverished movement during inspiration as well as poor postural stability. Postural instability may in turn reduce biomechanical efficiency of the diaphragm. Fixed abdominal contents needed for 'bucket handle' rib movement are not actually fixed, due to poor postural control of the abdominal muscles. Glottic dysfunction in people with HD (Heemskerk and Roos 2011) may also influence postural control and/or thoracic stability. These biomechanical deficiencies may reduce the capacity of the respiratory pump in people with HD.

3.3.2.4 Physiology of respiratory muscles

Force generation of the diaphragm in normal quiet breathing is achieved through recruitment of fatigue resistant slow and fast twitch muscle fibres and requires only 10-25% of the total force generating capacity, increasing to near maximal during coughing and sneezing (Mantilla and Sieck 2013), with fast type 2 muscle fibres being recruited with increasing levels of activity (Banner 1995). Within the human diaphragm, slow fibres make up approximately 55% of the fibres, with 21% being fast oxidative and 24% fast glycolytic. The proportion of slow fibres in the intercostal muscles is thought to be slightly higher than that of the diaphragm at 60% (Polla et al. 2004).

The ability of the slow fibres to maintain their contractile ability is due to their resistance to fatigue, which in turn is due to the balance between energy production and consumption. Slow oxidative fibres use little energy and the production of adenosine triphosphate in the mitochondria matches this. Fast glycolytic fibres require more adenosine triphosphate and also produce lactate as a by-product. Lactate and inorganic phosphates that are also a consequence of glycolytic fibre work, accumulate, causing fatigue. Performance loss is therefore quicker in fast fibres than in slow (Westerblad et al. 2010). Fatigable fibres are

selectively lost before fatigue resistant fibres in conditions that cause muscle atrophy e.g. chronic obstructive pulmonary disease with an increased proportion of slow twitch and decreased proportion of fast twitch fibres (Levine et al. 2013) which may impact in loss of force in expulsive acts such as coughing (Mantilla and Sieck 2013). Fatigue, as measured as lack of endurance of the respiratory muscles may be an important factor in respiratory failure. For the oxidative metabolism of the majority of the diaphragm muscle fibres to continue unceasingly, an adequate blood supply is necessary. The cross sectional area of diaphragm fibres is generally less than limb muscles, yet have a similar number of capillary vessels surrounding them. This ensures a more efficient oxygen supply to the diaphragm compared to other muscles (Polla et al. 2004).

Force generation in muscles in people with HD may be influenced by emerging evidence of altered membrane potential and hyperexcitability (Waters et. al. 2013), although this relationship is as yet not fully established. Skeletal muscle atrophy (She et al. 2011) and progressive loss of fast twitch fibres (Strand et al. 2005) in animal and human studies of HD pathology may impact on force generation in the respiratory muscles. This may have functional consequences during high respiratory demand activities and in cough efficacy. Low physical activity in people with HD (Quinn et al. 2013) may also influence muscle fibre atrophy as reduced respiratory muscle activity during controlled mechanical ventilation has been shown to decrease all fibre types in animal and human studies (Mantilla and Sieck 2013).

The physiology and biomechanics of the respiratory muscles enable them to continually produce forces that expand the thorax enabling ventilation of the alveoli and gaseous exchange. Impaired respiratory muscle strength can lead to decreased ventilatory capacity (Naeije 2005) and thus pulmonary function. These relationships were further explored in a large study (n=960 older people) (Buchman et al. 2008) that found correlations between respiratory muscle strength and pulmonary function ($r=0.46$ $p<0.001$). Further analysis, including measures of extremity muscle strength and mortality which were related, established that extremity muscle strength was a surrogate for respiratory muscle strength and that the association between respiratory muscle strength and mortality was mediated through pulmonary function. Buchman et al (2008) concluded that respiratory muscle strength is the beginning of a causal chain which leads to reduced pulmonary function and death. Physical activity is associated with higher FEV_1 whilst a sedentary lifestyle is associated with lower values. These findings were independent of confounders such as age, BMI and smoking habit

and may provide an important link between respiratory function and mortality (Jakes et al. 2002).

The relationship between respiratory and extremity muscle strength may help to explain decreased exercise capacity caused by deconditioning (Naeije 2005) with a potential cycle of inactivity, deconditioning, decreased peripheral and respiratory muscle strength, decreased pulmonary function and death. The exact causal relationships between these variables are unknown and likely to be confounded by pathology such as respiratory or neurodegenerative conditions, smoking habit, cognitive impairment, but the modelling by Buchman et al (2008) was not influenced by these confounders. In people with HD it is known that peripheral muscle weakness exists (Busse et al. 2008) and that physical activity levels are low (Quinn et al. 2013), yet it is not known whether respiratory muscle strength is reduced. It is therefore not known whether the underlying movement disorder results in decreased physical activity and thus reduced muscle strength and taking into consideration the cognitive and behavioural aspects of the disease, it is likely that more complex interdependent relationships exist.

Malnutrition influences both skeletal and respiratory muscles with animal studies showing decreased diaphragm muscle protein synthesis as a consequence of severe short term nutritional deprivation (Bando et al. 2012), causing a predominant shift from fast to slow fibre type (Ciciliot et al. 2013). In animal studies, force generation of the diaphragm after starvation was preserved and low frequency fatigue increased (Prezant et al. 1993), which is consistent with the change in fibre type. A small study of undernourished people with no pulmonary disease, found that expiratory muscle strength was linearly related to body weight and that both inspiratory and expiratory muscle strength were significantly reduced compared to well-nourished subjects (Arora and Rochester 1982). A similar association between malnutrition and decrease in expiratory muscle strength has also been found in people undergoing upper abdominal surgery (Lunardi et al. 2012).

Muscle atrophy may be a consequence of weight loss which is prevalent in HD (Aziz and Roos 2013) with evidence that in atrophied states, diaphragm weight loss is proportional to that of skeletal muscle (Polla et al. 2004). Some evidence exists in healthy subjects and people with cystic fibrosis and chronic obstructive pulmonary disease as to the positive relationship between diaphragm thickness and inspiratory muscle strength (DePalo et al. 2004; Enright et al. 2007; Vestbo et al. 2006). Despite evidence of weight loss and reduced BMI (Aziz et al. 2008; Djousse et al. 2002; Marder et al. 2009; Trejo et al. 2004) it is not known whether people with HD are malnourished. The European Huntington's Disease

Network recommend standards of nutritional care for people with HD, because of the impact of increased metabolic rate, swallow and feeding difficulties and high energy expenditure (Brotherton et al. 2012). These guidelines however are predominantly based on consensus of expert opinion as research evidence in this area is limited. If weight loss in people with HD does lead to respiratory muscle atrophy, this would decrease the capacity of the respiratory muscle pump.

3.3.2.5 Assessment of respiratory muscle strength

Respiratory muscle strength is usually measured in a global perspective, rather than as individual muscles, with mouth pressures being the most commonly used method (Polkey et al. 1995). Other methods include electrical and magnetic stimulation and invasive methods for specific measurement of diaphragm strength.

Volitional tests are simple to perform and do not cause much discomfort for subjects, although validity of the measures depends on the effort of the subject, therefore underestimation may be an issue (Celli and Grassino 1998). Understanding of the procedures is also dependent upon cognitive ability. Inspiratory and expiratory muscle strength may be measured by the maximum pressure that can be generated by the mouth; maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) respectively. This global measure not only reflects the pressure developed by the muscles, but also the passive elastic recoil of pressure of the lung and chest wall. At functional residual capacity, elastic recoil of the chest wall is zero, so the pressure at the mouth will equate to pressure generated by the muscles; at residual volume elastic recoil may contribute up to 30% of MIP and at total lung capacity (TLC) may contribute up to 40% of MEP. Although elastic recoil influences MIP and MEP at different lung volumes, the pressures tend to be measured at or close to RV and TLC respectively, as these lung volumes are easier to standardise between subjects compared to functional residual capacity (FRC) (American Thoracic Society/European Respiratory Society. 2002). For some subjects, particularly those with neuromuscular disorders, keeping a seal around the mouthpiece may be difficult and an alternative measure of pressure generated through the nostril may be used. The pressure generated through a maximal sniff, maximum sniff nasal inspiratory pressure (SNIP), is a relatively simple technique and may be used alongside yet not interchangeably with MIP (Iandelli et al. 2001; Uldry and Fitting 1995). Mouth and nostril pressures are easy to use clinical measures, but do not give specific information regarding diaphragm strength. This can be achieved by measuring the difference between oesophageal pressure and gastric pressure and is known as transdiaphragmatic

pressure. These measurements involve the passing of balloon catheters through the nose into the oesophagus and stomach and therefore require greater co-operation from the subject than that necessary for mouth pressure measurements (Celli and Grassino 1998). Severe diaphragm weakness can be assessed by comparing forced vital capacity (FVC) in both supine and sitting, with the former being 5-10% of the latter in healthy subjects, abnormal values being >30% (American Thoracic Society/European Respiratory Society 2002)

Non-volitional measures of respiratory muscle strength are specific to the diaphragm and can be carried out by stimulating the phrenic nerve electrically or magnetically. Electrical stimulation is carried out using surface or needle electrodes, the former having the disadvantage of stimulating pain as well as muscle activation, the latter carrying risk of trauma and infection. Magnetic stimulation is non-invasive and causes depolarisation of neural tissue in response to electrical fields generated by the magnetic pulses. It is preferable to direct electrical stimulation as larger fibres are activated, and not the smaller pain nerve fibres (Man et al. 2004).

Volitional measures of respiratory function are dependent on both the subject and the skill of the person conducting the measurement, the latter accounting for up to 12% variation in measures (Enright et al. 1994). Subject variability is high with standard deviations of 25-38% of mean values which makes comparison between studies difficult. Variability may be due to effort of the subject but respiratory function is correlated with gender, age and BMI and therefore predicted values are necessary for clinical and research purposes (Hautmann et al. 2000). Despite this variability, measurement of respiratory muscle strength has been found to be reliable for MIP: ICC 0.88-0.92 (Maillard et al. 1998), standard error 0.009 (Romer and McConnell 2004) and MEP: standard error 0.009 (Romer and McConnell 2004). Specifically, the Micro Respiratory Pressure Monitor device was found to be reliable in measuring mouth pressures in both standing (ICC 0.78-0.83, SEM 12-14, SDD 23-26) and sitting positions (ICC 0.86-0.90, SEM 9-10, SDD 18-22) (Dimitriadis et al. 2011).

There may be a learning effect in these volitional measures and an habituation period may be necessary when comparing repeated measures (Lomax and McConnell 2009) although the learning effect SNIP was found to be less than that of MIP in healthy subjects (Terzi et al. 2010). SNIP was found to be reliable in healthy subjects (ICC 0.85-0.92) (Maillard et al. 1998). It is recommended, based on a study with healthy subjects and people with neurodegenerative conditions that at least 10 sniff manoeuvres are taken to ensure reliable and valid results (Lofaso et al. 2006).

Respiratory muscle weakness is associated with increasing dyspnoea in people with MND/ALS and is thought to be related to both transmission and central drive deficits (Mustfa and Moxham 2001; Similowski et al. 2000). This finding is confirmed in people with myopathy who did not perceive inspiratory difficulty when breathing against increased inspiratory loads when compared to healthy subjects (Hours et al.2004). Dyspnoea is derived from physiological, psychological, sociological and environmental factors and as such can be measured as a sensory perception using the Borg scale and in terms of impact on activity using the modified medical research council (MRC) scale (Parshall et al. 2012). Although used extensively in people with respiratory conditions, the use of the MRC scale in people with neurodegenerative conditions is not recommended in people with exercise limiting limb weakness such as MND (Dougan et al. 2000). Its use may therefore also be limited in people with HD due to lower limb weakness (Busse et al. 2008) and cognitive impairment.

3.3.2.6 Assessment of respiratory muscle endurance

Respiratory muscle endurance is the ability to sustain ventilation against a load over time. This can be measured by calculating the pressure time product or the work of breathing. The pressure time product is normally measured over one minute and is calculated as the integration of pressure over time, i.e. the area under the pressure time curve of an inspiration or expiration. From this calculation, the mean pressure and ultimately the pressure time index can be calculated. Mean pressure over a breath cycle is calculated as:

Mean pressure = Pressure-time product/sampling period

The mean pressure can then be normalised by dividing it by the maximal pressure either MIP or MEP. This is then known as the pressure time index.

Pressure time index= mean pressure/MIP

The technique of measuring pressure should be noted as this will give an indication of whether the pressure time index refers specifically to the diaphragm or all respiratory muscles working against a load (pressure measured at the mouth) (American Thoracic Society/European Respiratory Society. 2002).

Methods of measuring respiratory muscle endurance are variable across studies and include: maximum voluntary volume in a specified time (12sMVV) (Leith and Bradley 1976); highest sustainable inspiratory pressure in a specified time (Nickerson and Keens 1982); heaviest load, incremental loading, tolerated for a specified time (McElvaney et al. 1989); length of time breathing against a maximal load (Hart et al. 2002; McElvaney et al. 1989) and single breath maximal work capacity (Enright et al. 2006a). The variety of methods demonstrates

the difficulty in accurately measuring endurance of the respiratory muscles in a range of populations. Clinically, a maximal incremental ventilation test is recommended (American Thoracic Society/European Respiratory Society. 2002).

Single-breath maximal work capacity is a method that does not require subjects to work to fatigue but measures pressure over time through a sustained maximal inspiration, i.e. through full range of respiratory muscle action (Ionescu et al. 1998). Single–breath work capacity correlates with diaphragm thickness in people with cystic fibrosis (Enright et al. 2007) and has also been found to be a reliable measure in this patient group (Enright et al. 2006a).

3.3.2.7 Respiratory muscle dysfunction in people with neurodegenerative conditions

Recent evidence suggests that respiratory muscle strength is decreased in people with early and mid-stage HD compared to matched controls (Reyes et al. 2014) but as this was not known when the framework was being developed; evidence from people with other neurodegenerative conditions was explored

Observational studies provide evidence of reduced respiratory muscle strength in people with MS. People with MS, n= 25, had significantly lower MIP (40.87cmH_2O ± 12.5) and MEP (51.62cmH_2O ± 26.8) compared to a matched healthy control group, n=15 (MIP 61.26cmH_2O ± 1.5, $p<0.001$; MEP 94.49cmH_2O ± 19.4, $p< 0.001$) (Koseoglu et al.2006). Abnormal percentage predicted values were found in studies with no comparator group, total n=128, MIP (27-77%predicted) and MEP (18-60%predicted) (Buyse et al. 1997; Gosselink et al. 2000; Mutluay et al. 2005). Nocturnal de-saturation was also noted in 70% of the people with MS (Buyse et al. 1997) with a mean S_aO_2 of 88.4%, in those that desaturated. This indicates a possible link between decreased respiratory muscle strength and decreased gaseous exchange leading to type 1 hypoxaemic respiratory failure. These studies covered a range of disease severity as measured by the expanded disability status scale (EDSS) with values ranging from 4.3 to 8.5, although a significant relationship between respiratory muscle strength and EDSS was only found in the study with all non-ambulatory participants and an EDSS of 8.5 (Gosselink et al. 2000). Exercise capacity as measured by VO_{2peak} was found to be significantly related to MEP and not MIP but also related to EDSS and functional scores (Koseoglu et al 2006) adding complexity to functional implications of the results. The use of % predicted values and absolute values between studies make comparisons difficult as inspiratory and expiratory muscle strength decrease with age (Lalley 2013).

Similar results have been observed in people with PD. People with mild-moderate PD, n= 35, had significantly lower MIP (29.6%predicted ±9.9) and MEP (41.8%predicted±12.6) than matched healthy controls, n=35, (MIP 77.7%predicted ±4.2; MEP 88.6%predicted±22.9) (Sathyaprabha et al 2005) with similar findings in people with ALS (Sathyaprabha et al. 2009).

The limited evidence suggests that the capacity of the respiratory muscle pump is reduced in people with neurodegenerative conditions which will impact on both lung volumes and ability to cough and effectively clear secretions. Decreased respiratory muscle strength can therefore impact on acute type 1 hypoxaemic respiratory failure in terms of clearing retained secretions and progressive decrease in lung volume. This progressive decline in lung volume will increase the load placed upon the respiratory pump and with a concurrent decrease in respiratory muscle strength lead to the development of type 2 hypercapnic respiratory failure.

3.3.3 Load placed on the respiratory muscle pump

Central respiratory drive, via intact transmission of impulses enables the respiratory muscles to ventilate the lungs, but this work must overcome intrinsic mechanical loads. The load may be: elastic, reflecting the physical properties of lung tissue and the chest wall; resistive, dependent upon patency of the airways and threshold which is dependent on end expiratory volumes (Hart 2008).

3.3.3.1 Elastic load

In healthy people, approximately two-thirds of the work of breathing is due to overcoming elastic load (Bach and Kang 2000). An increase in elastic load is related to the lung tissue and the chest wall. At the end of a normal expiration, i.e. at functional residual capacity (FRC), the inward elastic recoil of the lungs is matched by the outward elastic recoil of the rib cage (Ferguson 2006). Elastic recoil of the lungs is dependent upon the action of elastin with complete collapse of alveoli prevented by surfactant. Elastin as a complex protein structure acts to maintain airway patency as well as ensuring elastic recoil of the lungs. In respiratory lung disease such as emphysema, elastin fibre breakdown causes destruction of parenchyma with subsequent reduced airway compliance and airway collapse (Maclay et al. 2012). Proteases that destroy elastin are produced in inflammatory cells that may be stimulated by noxious substances such as cigarette smoke. Damage may be permanent as lung cells are unable to fully repair the elastic fibres leading to progressive lung disease (Shifren and Mecham 2006). Further damage may occur through repeated closure and re-opening of airways during tidal breathing causing sheer forces within the airways (Bian et al. 2010).

Although surfactant protects alveoli from collapsing at low volumes (Van Golde et al 1988) it is now understood that an optimal stretch magnitude exists for surfactant production. Over distention of alveoli e.g. during mechanical ventilation decreases surfactant production and conversely, a minor reduction in stretch from optimum reduces production leading to decreased compliance, further decreased stretch and eventual collapse of alveoli (Amin et al. 2013). Lack of periodic deep breaths may therefore lead to micro atelectasis (Bach and King 2000) which could be a consequence of a sedentary lifestyle. Alveolar collapse leading to atelectasis will result in reduced lung volume and subsequent decreased lung compliance (Dargaville et al. 2010), thus increasing elastic load.
The high incidence of smoking (Byars et al. 2012) and low activity levels (Quinn et al. 2013) of people with HD may lead to an increased elastic load within the respiratory system due to destruction of elastin and micro atelectasis respectively.

Age influences both lung tissue and chest wall compliance. The closing volume, the lung volume at which small airways begin to close, increases with advancing age which increases elastic load, although most of the compliance related changes are due to decreased chest wall compliance and decreased respiratory muscle strength (Lalley 2013). Age should therefore be considered as a confounder in observation studies of respiratory function.
Lung volumes are also reduced by kyphotic postures (Harrison et al. 2007) in particular FVC and peak expiratory flow rate (PEFR) (Lin et al. 2006) and tidal and minute volumes (Landers et al. 2003). This may be due to the decrease in physical size of the thorax or be related to underlying muscle weakness associated with the kyphosis. In these instances, FEV_1 will also be low, but in proportion to FVC, and a restrictive respiratory pattern is noted (West 2008a). The dystonic flexed trunk postures noted in people with HD (Louis et al. 1999) may reduce the physical size of the thorax, but the impact on lung volume may depend on time spent within these postures.
Sufficient inspiratory muscle capacity is needed to move the ribs, maintain rib joint integrity and maintain chest wall compliance (Bach and Kang 2000) and maintain the respiratory muscles' postural role (Bianchi and Gestreau 2009). Chest wall compliance is also influenced by changes in posture due to alterations of range of movement available in rib cage joints (Lee et al. 2010). Gross changes in posture from the upright sitting position through to supine lying show a decrease in rib cage movement as the body becomes more horizontal. Concurrent with the decreased rib cage movement, changes in tidal volume and minute ventilation can be observed (Romei et al. 2010). Subtle changes in the upright sitting position

also influence movement of the chest wall, with postures that would be thought to reduce compliance in one region, involve increased movement elsewhere in the chest wall. These changes ensure that overall efficient ventilation is maintained despite changing the elastic load on the respiratory system (Lee et al. 2010). Elastic load on the respiratory system is dependent upon the compliance of the lung tissue and the chest wall, which in turn are influenced by lung volume and posture. In people with HD, recent evidence demonstrates that people with HD have reduced lung volumes compared to matched control participants (Reyes et al. 2014). This may be due to atelectasis as a result of known decreased physical activity (Busse et al. 2009; Quinn et al. 2013) and postural changes due to bradykinesia and dystonia with subsequent rigidity of chest wall muscles and decreased chest wall compliance leading to an increased elastic load on the respiratory pump. These theoretical assumptions will be explored in the following section which reviews evidence regarding lung volumes in people with PD, MS and MND/ALS.

3.3.3.2 Lung volumes in people with neurodegenerative conditions

Forced vital capacity (FVC), the maximal amount of air in a forced expiration following a maximal inspiration is a measure of inspiratory capacity and expiratory reserve volume (Cotes et al. 2006). In people with mild to moderate PD, n=35, FVC was decreased (56.0%predicted±14.5) compared to matched healthy controls n=35 (84.2%predicted±14.6) (Sathyaprabha et al. 2005) and was found to be significantly lower than predicted values in people with moderate PD (Sabate et al. 1996). Conflicting results were found in people with mild to moderate PD with no difference between actual and predicted values (Canning et al. 1997). This study included 16 participants and may have been underpowered. Decreased FVC (49.6%predicted±18.9) was also observed in people with ALS n= 40 compared to healthy controls n=63 (84.6%predicted±14.8). Concurrent with the decreased FVC was a decrease in forced expiratory volume in one second (FEV_1) and a significant increase in FEV_1/FVC indicating a restrictive respiratory pattern (Sathyaprabha et al. 2009). Although there was an increase in FEV_1/FVC in people with PD (91.3±8.4) compared to healthy control subjects (86.0±10.1) this was not significant (Sathyaprabha et al. 2005), with Sabate et al (1996) noting that 27% of people in their study did demonstrate a restrictive pattern. A limitation of the studies was the exclusion of smokers which although removes the confounding variable of airway disease, may demonstrate reduced external validity.

There is little evidence of reduced lung volume in people with MS, except for during the late stages of the disease. Gosselink et al. (2000) observed FVC%predicted values of 43±26 in a

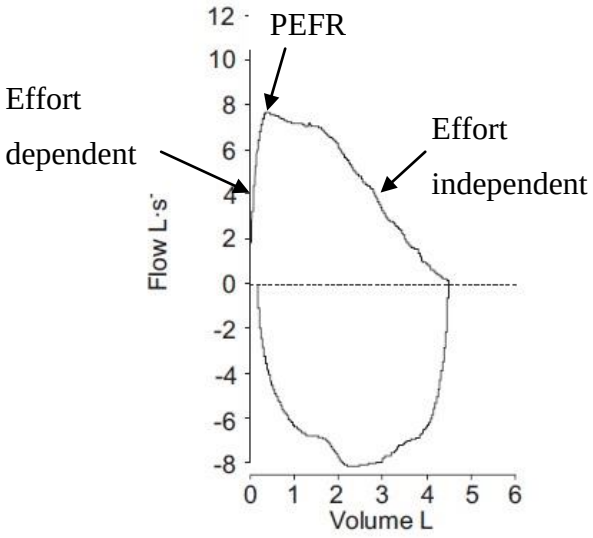
group of 28 non-ambulatory people with MS. A study of people with mild to moderate disease n=40, stated that a significant difference existed between people with MS and predicted value but the method for analysis was unclear. The FVC%predicted value of 94±12 would question whether this was in fact a clinical difference (Mutluay et al 2005). A comparative study with healthy control subjects (Koseoglu et al. 2006) and two single group studies (Altintas et al. 2007; Foglio et al. 1994) showed no statistically significant difference to predicted values of FVC.

These studies indicate that decreased lung volume is a feature of PD and ALS which may relate to rigidity and decreased peripheral muscle strength respectively and alters the biomechanics of breathing resulting in a restrictive respiratory pattern. In people with MS however, lung volume appears to be maintained despite decreased respiratory muscle strength until the late stage of the disease, which may indicate progressive atelectasis that contributes to type 2 hypercapnic respiratory failure. Decreased lung volume will increase elastic load concomitant with a decrease capacity and thus pre-dispose people with neurodegenerative conditions to type 2 hypercapnic respiratory failure. As a consequence of this knowledge, the European guidelines for the management of ALS recommend monitoring of FVC with a value of <80%predicted being one of the criteria for intervention with non-invasive ventilation (Andersen et al 2012).

3.3.3.3 Resistive load

Resistive load refers to the work that needs to be done to overcome resistance to airflow, particularly during expiration. This resistance is common in conditions that include bronchospasm or upper airways obstruction (Hart 2008). Normal expiratory airflow is the result of elastic recoil of the lungs, with forced expiration requiring abdominal and intercostal muscle involvement (Banner 1995). These muscles generate airflow up to a peak value seen on expiration from total lung capacity and therefore this measurement of peak expiratory flow rate (PEFR) is effort dependent. After this point, flow plateaus and is linear to lung volume, driven by the elastic recoil of the lungs and therefore independent of effort (Cotes et al. 2006). This is illustrated in Figure 2. PEFR reflects large airway calibre, whereas the similar measure FEV_1 reflects small airway calibre.

Figure 2 Normal flow volume loop (adapted from Miller et al 2005, p327)



PEFR peak expiratory flow rate

The flow volume loop can identify obstructive and restrictive respiratory conditions based on the shape of the graph, FEV_1%predicted value, and FEV_1/FVC. The flow volume loop in Figure 3 identifies a low FEV_1 and PEFR, with the effort dependent portion of the curve being concave representative of an obstructive lung disorder. A restrictive respiratory condition is illustrated in Figure 4 by a low FEV_1 and low FVC with flow being higher than expected at a given volume (Pellegrino et al. 2005).

Figure 3 Flow volume loop identifying an obstructive lung condition

From: Pellegrino et al. 2005, p 954

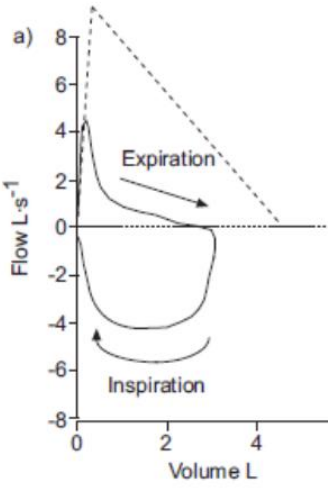
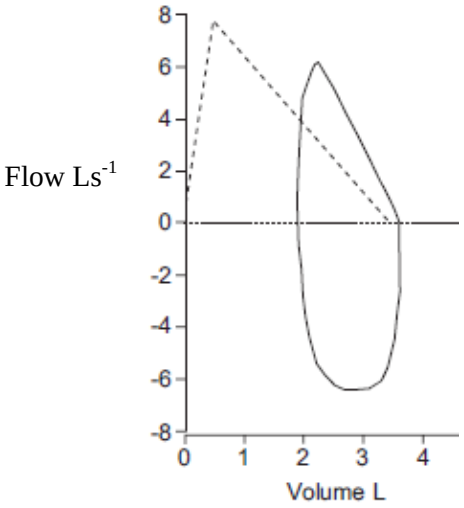


Figure 4 **Flow volume curve identifying a restrictive respiratory condition**

From: Pellegrino et al. 2005 p 954

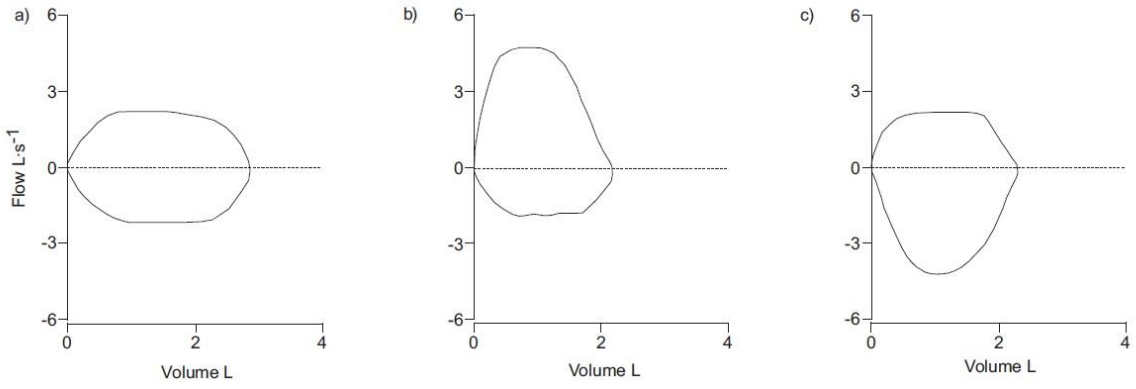


Increased resistance to airflow can be due to retained secretions obstructing the airway e.g. aspiration pneumonia (Ebihara et al. 2012) or airway thickening e.g. chronic obstructive pulmonary disease (Kosciuch et al. 2009). Airflow limitation is assessed by FEV_1% predicted as indicated in the classification of COPD by the Global Initiative for Chronic Obstructive Lung Disease (GOLD): mild ≥ 80%predicted; moderate 50% ≤ FEV_1 < 80%predicted; severe 30% ≤ FEV_1 < 50% predicted; very severe < 30%predicted (Vestbo et al. 2013).

These obstructions describe dysfunction within the lower airways of the lung, but for people with neurodegenerative conditions consideration also needs to be given to the upper airways, in the particular the vocal cords and glottis. A categorisation of extrathoracic i.e. above the sternal notch and intrathoracic i.e. below the sternal notch (Pellegrino et al. 2005) can be used to identify areas of dysfunction in flow volume loops, see Figure 5 for characteristic patterns.

Figure 5 **Flow volume loops for intrathoracic and extrathoracic obstruction**

From Pellegrino et al. 2005, p960



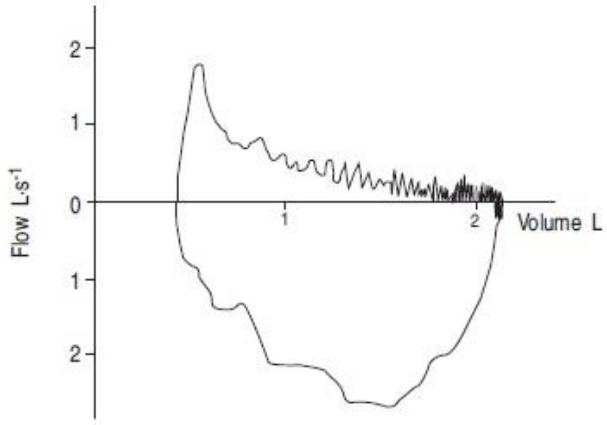
a) b) c)

The normal inspiratory curve is lost when extrathoracic structures e.g. pharynx, larynx are obstructed, as in a) and b) above, whereas the expiratory curve is lost when intrathoracic structures e.g. main bronchi are obstructed, see a) and c). When both inspiratory and expiratory flow is obstructed as in a), this suggests a fixed central or upper airway obstruction. These characteristic loops can only be used for diagnosis if the subject's effort is maximal (Pellegrino et al. 2005). The loops can also be assessed by examining the mid flow ratio of inspiration and expiration i.e. the ratio of maximal expiratory to maximal inspiratory flow at 50% of vital capacity (Miller and Hyatt 1973). The mid flow ratio (MEF_{50}/MIF_{50}) can be categorised as approximately 1 in fixed obstructions Figure 5a, >1 in extrathoracic obstructions Figure 5b and <1 intrathoracic obstructions Figure 5c. Central or upper airway obstruction can also be assessed by the ratio of FEV_1 to PEFR, a value of >8 suggesting central or upper airway obstruction (Pellegrino et al. 2005).

3.3.3.4 Airflow limitation in people with neurodegenerative conditions

There is little evidence of lower airway flow limitation in people with neurodegenerative conditions. In people with PD and ALS, FEV_1 is significantly reduced compared to healthy control subjects. but the reduction is concomitant with significantly reduced FVC and therefore represents a restrictive rather than obstructive pattern (Sathyaprabha et al. 2005; Sathyaprabha et al. 2009). Sabate et al (1996) report obstructive ventilatory dysfunction in 54% of a sample of 58 people with PD, but lack of data in the results meant that it is not clear whether this was due to upper or lower airway obstruction. Normal FEV_1 values have been described in people with MS (Altintas et al. 2007; Foglio et al. 1994; Koseoglu et al 2006). Mutluay et al (2005) however report a significant reduction in FEV_1% predicted with a value of 91% for the sample, although this would be considered mild using the GOLD classification if accompanied by other signs and symptoms (Vestbo et al 2013).
Large airway obstruction as measured by PEFR was reduced in people with PD and ALS but not in MS (Koseoglu et al. 2006; Sathyaprabha et al. 2005; Sathyaprabha et al. 2009). The reduction in PEFR may represent upper airway obstruction which can be observed from flow volume curves. In people with neurodegenerative conditions oscillations may occur during inspiration and expiration and are thought to be due to vocal cord tremor or instability of the upper airway (Buyse 2006; Vincken et al. 1986), see Figure 6 for a flow volume curve with expiratory oscillations found in PD. Vocal cord dysfunction may also be observed by truncation of the loop and flattened inspiratory curves (Watson et al. 2009).

Figure 6 Flow volume curve in Parkinson's disease (Buyse et al 2006, p268)



People with HD may have an increase in resistive load as a consequence of upper airway obstruction, as pharyngeal and laryngeal dysfunction has been observed in dysphagia (Heemskerk and Roos 2011) and speech studies (Velasco García et al. 2011; Vogel et al. 2012), with Rusz et al. (2013) observing turbulent airflow through the vocal cords. As a consequence of swallow difficulties, aspiration does occur and obstruction in the lower airways would lead to increased resistive load.

3.3.3.5 Threshold load

Intrinsic positive end expiratory pressure is created if expiration stops before the lung volume has returned to functional residual capacity (FRC). This is also known as dynamic hyperinflation and auto positive end expiratory pressure (Lumb 2010). In people with airflow limitation e.g. chronic obstructive airways disease, the resistance to expiratory airflow lengthens the time needed to exhale a given volume of air. If inspiration commences before the lung has returned to FRC, air trapping will occur. The increased end expiratory lung volume alters the relationship between the elastic recoil of the lungs and that of the chest wall, which increases the work of breathing (Ferguson 2006). It is necessary for each breath to overcome this load and it is therefore termed 'threshold load' and is common in moderate to severe obstructive respiratory disorders. Although air trapping to the extent of that in emphysema is unlikely in people with HD as severe airway obstruction is not noticed clinically, alteration in breathing pattern generation may cause expiration to stop before lung volume has returned to functional residual capacity. The extent of the increased threshold load would depend on the extent and type of breathing pattern alteration.

3.3.3.6 Extrinsic load on the respiratory system

Elastic, resistive and threshold loads represent intrinsic factors that increase the work of breathing. Additional load can be placed on the respiratory system from extrinsic sources including chemical e.g. hypercapnia and metabolic e.g. exercise. Hypercapnia is detected by chemoreceptors stimulating the central respiratory controller to increase neural drive to the respiratory muscles (Hill and Eastwood 2011). Chronic hypercapnia is common in people with neurodegenerative conditions caused by decreased capacity and increased elastic load (Misuri et al. 2000) thus a cycle of decreasing capacity and increasing load may lead to respiratory failure. In people with PD and MS, the respiratory drive response to hypercapnia is impaired (Seccombe et al. 2011; von Klaveren et al. 1999); the increased load is not matched by increased drive, which in the presence of respiratory muscle weakness will lead to respiratory failure.

During exercise, CO_2 and metabolite production increases and homeostasis is maintained through chemoreceptor, baroreceptor and proprioceptive input. Exercise therefore increases the load on the respiratory pump, particularly at high intensities when respiratory metabolites redistribute blood away from locomotor muscles and preferentially to respiratory muscles (Dempsey 2012). Functional exercise capacity is reduced in MS (Bosnak-Guclu et al. 2012) and PD (Canning et al. 2006) and this may be due to a combination of factors including decreased capacity, increased load and impaired response to hypercapnia. This low level of activity may actually mask symptoms of respiratory dysfunction such as dyspnoea (Haas et al. 2004). There is little known about the physiological response of people with HD to exercise with a small study in people with early HD noting a reduced workload during sub maximal exercise testing compared to control (Jones et al. 2012).

3.3.3.7 Assessment of load on respiratory system

The elastic load placed on the respiratory system is due to the compliance of both the lungs and the chest wall. The total compliance is therefore the summation of these two factors as below:

1/compliance (thorax) = 1/compliance (lung) + 1/compliance (chest wall)
(Cotes et al. 2006)

Chest wall compliance is derived from separate static measurements of thoracic and lung compliance. Compliance is measured as the slope of the pressure (pleural)-volume curve created from repeated inspirations and expirations at different lung volumes. For static lung compliance the repeated manoeuvres are voluntary breaths, whereas for thoracic compliance

the respiratory muscles are relaxed and manoeuvres are pre-set via positive pressure breathing apparatus (Cotes et al. 2006).

Resistive load may be measured by techniques that measure resistance to airflow such as FEV_1; FEV_1/FVC% and PEFR. FEV_1 and FVC are measured in the same manoeuvre – a forced expiration from total lung capacity. FEV_1 is the volume of air expired in the first second of the forced expiration and is usually reported as a percentage of FVC, the maximum volume of air expired. This then standardises FEV_1 as it is related to gender, height and age; the normal ratio being 70-80%. These measures are effort dependent and visually examining the flow volume curve will highlight airway obstruction. When airways are obstructed, the linearity is lost and the curve may become concave. From the flow volume curve, the mid expiratory flow rate, $FEF_{25-75\%FVC}$ can be measured as an index of the average flow over the middle half of the forced expiration. This part of the manoeuvre is effort independent and is used for detecting early stages of airflow limitation (Miller et al. 2005).

Peak expiratory flow rate can also be measured independently from FEV_1 and FVC. The flow rate is dependent on effort and mechanical properties of the lungs as well as airways' resistance. It tends to be a better measure of large airway obstruction, whereas FEV_1 is a better measure of small airways calibre (Cotes et al. 2006). Airway obstruction may also occur in the pharynx, larynx, trachea and main bronchi, which is referred to as upper and central airway obstruction. This type of obstruction does not reduce FEV_1 but does reduce PEFR, and a FEV1/PEFR ratio of >8 is suggestive of central or upper airway obstruction (Pellegrino et al. 2005).

Threshold load is that created when intrinsic positive end expiratory pressure is present and can be determined from the negative inflection in oesophageal pressure from the point of inspiratory effort to the point of zero flow (Haluszka et al. 1990). Haluska et al (1990) found a significant correlation between intrinsic positive end expiratory pressure and FEV_1; measurement of airways obstruction may be an indirect way, therefore, of assessing the threshold load on the lungs.

3.3.4 Factors influencing respiratory function

The preceding section has identified potential impairment in respiratory function in people with HD and highlighted factors that may influence or be influenced by respiratory function. Smoking (Shifren and Mecham 2006) and age (Lalley 2013) affect respiratory function and therefore may be confounders in observation studies. Factors specific to HD that may influence respiratory function are swallow, posture, exercise capacity and physical activity.

Impaired swallow will lead to aspiration and potential type 1 hypoxaemic respiratory failure with laryngeal and pharyngeal dysfunction potentially increasing resistive load on the respiratory pump. Breathing and swallow are highly integrated activities controlled by neural interactions in the brainstem and connections to the cranial nerves (Hårdemark Cedborg et al. 2009) and exploration of both functions may provide insight into dysfunction within the brainstem and neural control of breathing.

Dystonia and bradykinesia will lead to a flexed posture which in turn can reduce lung volume (Harrison et al. 2007) and alter the biomechanics of the respiratory muscles and compliance of the rib cage (Lee et al. 2010) inducing both increased load on and decreased capacity of the respiratory muscles.

The relationships between respiratory function, physical activity and exercise capacity are complex. Physical activity is reduced in people with HD (Quinn et al. 2013) but little is known regarding exercise capacity and respiratory function. In studies from the general population, deconditioning caused by decreased exercise capacity (Naeije 2005) may lead to decreased peripheral muscle strength which is related to respiratory muscle strength (Buchman et al. 2008). Decreased physical activity in people with HD may lead to decreased capacity of the respiratory pump and conversely decreased respiratory muscle strength may reduce physical activity. Exercise may increase the extrinsic load placed on the respiratory pump and/or decreased capacity of the pump may reduce exercise capacity.

The influence of swallow, posture, physical activity and exercise capacity therefore needs to be explored in people with HD in order to help explain any change in respiratory function. The following section explores methods of measurement of the key factors potentially influencing respiratory function in people with HD.

3.3.4.1 Measurement of swallow

Normal swallow comprises a number of stages: oral, pharyngeal, laryngeal and oesophageal (Heemskerk and Roos 2011; Hughes and Wiles 2000). Clinical assessment evaluates the oral phase and differential diagnoses of the pharyngeal, laryngeal and oesophageal phases which can then be evaluated by assessments such as videofluoroscopy or ultrasound. Clinical assessment includes gathering signs and symptoms through history taking, cranial nerve assessment and observation of swallow (Gates et al. 2006). Videofluoroscopy and ultrasound can then clarify the mechanism of the swallow problem irrespective of the pathology causing the problem (Hughes and Wiles 2000).

Videofluoroscopy is the most common tool for evaluating all stages of swallow. It is carried out by administrating a radiopaque liquid e.g. barium, mixed with liquid and food with radiographic images recorded during swallow for analysis (Gates et al. 2006). Although videofluoroscopy is recommended as the 'gold standard' in identifying swallow dysfunction (Wu et al. 2004), it may not be suitable for assessing progressive swallow dysfunction due to repeated radiation. An alternative assessment is a timed swallow test that can be carried out with minimal equipment and training (Nathadwarawala et al. 1992).

The timed swallow test requires a subject to swallow 150ml of cold water as quickly as possible, while the time and number of swallows is measured. The volume of water may be adjusted if subjects are predicted to have difficulties with 150ml. This test has been shown to have reliability and validity in a group of people with neurological problems (Nathadwarawala et al. 1992).

3.3.4.2 Measurement of posture

Quantification of spinal and head posture is a complex activity as it is a three dimensional entity. The spine in standing position normally has lumbar and cervical lordoses and a thoracic kyphosis whereas in the sitting position, there is no consensus as to what good or normal posture is. Qualitatively, ideal sitting posture may be one of three options: a flat lower thoracic and lumbar posture; flat lumbar posture with back rest and lordosis at both lower thoracic and lumbar regions (Claus et al. 2009). The majority of research on spinal posture relates to back and neck pain as well as correction of spinal deformities. The purpose of measurement of posture in this study was to investigate relationships between thoracic, neck and head postures with respiratory function and therefore the emphasis was on feasible, reliable measures of posture rather than comparison with normal values.

Measuring true spinal posture requires radiographic images and subsequent quantification of angles. Although this would appear to be the 'gold standard', error can occur with identification of bony landmarks and incorrect drawing of lines for angle determination (Gstoettner et al. 2007). This method also has the disadvantage of requiring subjects to undergo radiation. Surface methods of determining posture have therefore developed and include goniometers; inclinometers; flexicurve; computerised movement analysis; spinal wheel and photographs.

Clinically, instruments such as goniometers, inclinometers and flexicurve are used with reliability dependent upon the examiners experience in using the device as well as their ability to identify bony landmarks (Sheeran et al. 2010).

Computerised movement analysis uses sensors attached to the skin, corresponding to bony landmarks, to determine spinal curvature. Magnetic tracking devices such as Fastrak® use a source of pulsed electromagnetic waves and up to four sensors attached to bony landmarks. The angle and distance from the sensor are sampled and angles computed by software to provide a three dimensional analysis of posture and movement (Jordan et al. 2000). Although this system is accurate and reliable, it is still subject to error in positioning of sensors (Sheeran et al. 2010) and the proximity required for the sensors. Other devices such as accelerometers are also used to measure posture when acceleration is zero, and have been assessed to be accurate and reliable in the sitting position (Wong and Wong 2008). Novel instruments such as the spinal wheel (Sheeran et al. 2010) and the spinal mouse (Mannion et al. 2004) have also demonstrated reliability in measurement of posture.

Analysis of posture from photographs is suggested as an alternative 'gold standard' to radiographic imaging (van Niekerk et al. 2008). Intra-tester reliability was assessed, in a sample of 39 adolescents, within one day and concurrent validity was assessed by comparison with a radiographic image using a digital low dose radiography device.

Measurements were taken of sagittal head angle, the angle between the horizontal and a line drawn between the lateral canthus of the eye and midpoint of the tragus; cervical angle, the angle between the horizontal and the line drawn between the midpoint of the tragus and the spinous process of C7; thoracic angle, the angle between the line drawn between the spinous process of C7 and the manubrium and the line drawn between the spinous process of T8 and the manubrium. Protraction/retraction of the shoulder and arm angles were also calculated. Bland Altman limits of agreement were calculated, with small bias in cervical, head and thoracic angles (-1.12º, -1.56º, -1.12º respectively). Concurrent validity was high with Pearson correlation coefficients between photographs and radiographs of 0.84, 0.89 and 0.92 for head, cervical and thoracic angles. Van Niekerk et al (2008) however, did note that there were some difficulties in visualising markers and made recommendations to improve the protocol for data collection.

Analysis of photographs for quantification of posture has been carried out using protractors and digitisation. Watson and Trott (1993) assessed head angle using a protractor and plumb line, though Dunk (2005) suggests that using a biological marker is preferable to external markers such as the plumb line. Researchers have also used bespoke software packages for digital analysis of photographs (McEvoy and Grimmer 2005; van Niekerk et al. 2008). Despite technological advances, reliability of postural measurements is variable and validity studies are few. Reliability of measurement is dependent upon anatomical knowledge for the

placement of markers on bony landmarks, standardisation of subject positions and human error in visualising markers on photographs. Validity is also dependent on marking of bony landmarks and the movement of skin after placement. Morl and Blickhan (2006) note that although markers and movements of the lumbar back surface are not identical to positions and movements of the lumbar vertebrae, surface markings can predict vertebral position and movement.

3.3.4.3 Measurement of exercise capacity

The ability or capacity to exercise is dependent upon the integration not only of the cardiovascular and respiratory systems but also of the blood, neurological, psychological and skeletal systems (Goldstein 1990). Measurement of exercise capacity therefore needs to include all these systems within the test. The following section will review methods of assessing exercise capacity and relate this to people with neurological conditions.

Exercise testing usually refers to an individual's capacity for maximal long term exercise, involving the aerobic energy system. Tests for immediate and short term energy systems do exist, but are specific to sports people who use these energy systems. Maximal oxygen consumption ($\dot{V}O_{2max}$) is the fundamental measure of physiological functional capacity for exercise, but since its inception as a concept of cardiovascular capacity the method of attaining maximal activity has been questioned (Mitchell et al. 1958). $\dot{V}O_{2max}$ can be assessed through a variety of exercise tests that use the body's large muscle groups and include treadmill walking or running; stationary bike and step tests. Protocols for increasing workload may be continuous i.e. incremental increases in exercise without rest and discontinuous i.e. with rests between increments, both types producing similar $\dot{V}O_{2max}$ values (Duncan et al. 1997). The American College of Sports Medicine guidelines recommend $\dot{V}O_{2max}$ as the criterion measure of cardiorespiratory fitness but acknowledge that when direct measurement is not feasible, submaximal exercise tests can be used as estimation (American College of Sports Medicine. 2010). For people with clinical conditions, $\dot{V}O_{2peak}$ is often used as an estimate for $\dot{V}O_{2max}$ (American Thoracic Society American College of Chest Physicians. 2003).

$\dot{V}O_{2max}$ testing requires a range of equipment including treadmill/cycle ergometer as well as a computerised system that collects and analyses data from a flow meter and gas sampling chamber. A number of field tests have therefore been developed that can be used within a clinical setting and can measure exercise capacity in people with limitations in one or more body systems.

The six minute walk test (6MWT) is a self-paced walk on a 100 foot hallway and evaluates the response of cardiovascular, respiratory, blood, neurological, psychological and skeletal systems to exercise (American Thoracic Society. 2002). It was developed from and is highly correlated with the 12 minute walk test and provides a feasible option for the measurement of exercise capacity (Butland et al. 1982). When compared to 2MWT and 12MWT tests, the 6MWT is better tolerated and more reflective of activities of daily living and is seen as the test of choice for clinical or research purposes (Solway et al. 2001).
The 6MWT is recommended for a range of neurological conditions (Tyson and Connell 2009) and has been assessed for reliability and validity specifically in people with MS and PD. Reliability in people with MS and PD is excellent with ICC ranging from 0.91 to 0.96 (Falvo and Earhart 2009; Fry and Pfalzer 2006; Goldman et al. 2008; Schenkman et al. 1997). Savci et al (2005) and Canning et al (2006) both demonstrated significant differences between people with MS and PD with healthy controls, indicating construct validity for 6MWT in these populations. The 6MWT has been found to be reliable in people with pre-manifest and manifest HD, ICC 0.98 and 0.94 respectively and have a minimal detectable change of 36.22m (pre-manifest HD) and 86.57m (manifest HD) (Quinn et al. 2013). The Physiotherapy Clinical Guidelines for Huntington's disease, by consensus, suggests the 6MWT as an outcome measure for exercise capacity (Quinn and Busse 2012).

3.3.4.4 Measurement of physical activity

Physical activity is defined as "any bodily movement produced by skeletal muscles that requires energy expenditure" (World Health Organisation. 2012). Physical activity includes a range of activities such as household chores, walking to the shops/work, physical work, recreational activity and exercise and thus presents a complex activity to measure accurately. A range of tools have been devised that attempt to quantitatively capture physical activity, a summary of which is provided below.

Accelerometers are electromechanical devices that can measure acceleration in one, two or three dimensions. A simple pedometer will measure how many steps a person takes per day, but they are limited by not taking into consideration the person's movement style and walking speed (Busse et al. 2004). Step activity monitors are more technologically advanced devices and measure overall activity levels and patterns of activity as well as step count. Reliability studies demonstrate good to excellent intraclass correlations for people post stroke, ICC 0.95 (Rand et al. 2009), PD, ICC 0.45-0.96 (White et al. 2007) and a mixed

group of post stroke, PD, MS and healthy subjects, ICC 0.68-0.85 (Hale et al. 2008) and a mixed group of people with MS, PD and primary muscle disorder, ICC 0.82-0.94 (Busse et al. 2004). Standard error of measurement ranged between 23-33% (Busse et al. 2004; Hale et al. 2008; Rand et al. 2009).

In people with neurological conditions, step activity monitors have demonstrated good criterion validated against gait parameters (Esliger et al. 2007; Schmidt et al. 2011). Construct validity, assessed by measuring activity in groups known to be different was demonstrated by Busse et al (2004) and Schmidt et al (2011). Waist worn devices are suggested to be a more valid measure of activity as they are placed closer to the centre of mass and capture whole body movements (Motl et al. 2010). Although activity monitors accurately quantify activity, they do not give an indication of the type of activity carried out. These domains of physical activity can be assessed through a range of questionnaires.

Physical activity questionnaires can be used for many purposes including surveillance, as an outcome measure in intervention studies and investigating relationships between disease and physical activity (Ainsworth et al. 2012). A systematic review on reliability and validity of physical activity questionnaires evaluated 96 papers which tested 130 questionnaires for a range of age groups. The majority of questionnaires showed acceptable to good reliability (ICC 0.64-0.79), though criterion validity was generally low (median Spearman 0.30, Pearson 0.46). Criterion validity was assessed against other questionnaires, accelerometry and the doubly labelled water method. This review identified four questionnaires that showed acceptable to good results for both reliability and validity: International Physical Activity Questionnaire (IPAQ) – short form; Flemish physical activity computerised questionnaire; previous day physical activity recall and the recess physical activity recall (Helmerhorst et al. 2012).

The Flemish physical activity computerised questionnaire measures activity in the domains of physical activity, job, leisure time, household chores, transport and personal care over a typical week in adults, with primary outcomes of total hours of activity per week and metabolic equivalent of task (MET) (Matton et al. 2007). Completion requires access to a computer and currently the questionnaire is only available in Dutch, although English, Portuguese and French versions are being developed (Scheers et al. 2012). Similar domains are measured in the recess physical activity recall (Martínez-Gómez et al. 2010) and the previous day physical activity recall questionnaires (Weston et al. 1997) except for occupation as these questionnaires are aimed at adolescents.

IPAQ-s gathers data on three specific levels of activity over the last seven days: walking, moderate intensity and vigorous intensity undertaken in the leisure, domestic, occupation and transport domains in adults. The questionnaire is available in 23 languages, a number of which have been evaluated internationally for reliability and validity (Craig et al. 2003). Data from across 12 countries were collected on: test-retest reliability; concurrent validity between versions and criterion validity against accelerometer data. The results found that the short and long forms of the questionnaire were reliable with Spearman correlation coefficients of 0.76 and 0.81 respectively. Concurrent validity between the different versions was reasonable, r= 0.67 with fair to moderate agreement between long and short forms with accelerometer data. The conclusions of this study were that the short form recording activity over the last seven days was feasible to administer, reliable and valid to use with adults aged 15-69 and the long form could be used when more detail of the activities were needed for research purposes. IPAQ has been found to have good reliability in people with manifest HD with a minimal detectable change of 2792 MET min/week (Quinn et al. 2013) and that it is valid for discriminating between healthy controls and people with manifest HD (Khalil 2012). The purpose of IPAQ is for epidemiology studies and not for intervention studies, but is suggested as a useful questionnaire to gather data on activity levels in people with Huntington's disease (Quinn and Busse 2012).

3.4 A conceptual framework of respiratory failure in people with Huntington's disease

The previous chapters have reviewed the literature regarding the pathological changes occurring in HD and, using the categorisation of respiratory failure described by Hart (2008), literature related to respiratory function and the relationship with respiratory failure in people with neurodegenerative conditions. The synthesis of this information provides a framework to explore respiratory function in order to understand respiratory failure in people with HD which is illustrated in Figure 7 and Figure 8. The framework is underpinned by theoretical postulation from what is known in HD and empirical evidence from people with PD, MS and MND/ALS. Although the framework has been divided into two distinct types of respiratory failure, progressive decline in lung volume may be a causal link in progression from type hypoxaemic respiratory failure to type 2 hypercapnic respiratory failure.

People with HD may develop acute hypoxaemic respiratory failure due to respiratory infection and aspiration pneumonia, the most common cause of death in people with HD (Heemskerk and Roos 2010). Airway clearance may be impaired as evidenced in people with

MS (Aiello et al. 2008) and PD (Ebihara et al. 2003) compounding the problem of retained secretions and consequent impaired diffusion of gases. Smoking (Shifren and Mecham 2006), age (Lalley 2013), dystonic posture (Louis et al. 1999) and subsequent rigidity of the chest wall and low physical activity levels (Quinn et al. 2013) may result in alveolar hypoventilation and decreased lung volumes as seen in people with PD ((Sabate et al. 1996). Both alveolar hypoventilation and aspiration pneumonia will result in ventilation perfusion mismatch and potential type 1 hypoxaemic respiratory failure.

The conceptual framework proposes a number of ways in which type 2 hypercapnic respiratory failure may occur in people with HD which spans all three elements of drive, capacity and load. Automatic breathing generated within the pontomedullary region of the brainstem may be altered as a consequence of neuronal degeneration (Rub et al. 2014) and atrophy (Hobbs et al. 2010) due to the presence mutant Huntingtin (Herndon et al. 2009) leading to the altered pattern observed at rest (Fischer et al 1983; Leopold et al. 1985). Evidence of lack of integration of breathing and swallowing (Heemskerk and Roos 2010; Heemskerk and Roos 2011; Kagel and Leopold 1992) may point to central pattern generation dysfunction. A reduced response to hypercapnia and abnormal occlusion pressures in people with PD (Seccombe et al. 2011) suggests that similar findings could be found in people with HD.

Capacity of the respiratory muscles may be decreased due to biomechanical and physiological changes leading to decreased respiratory muscle strength, similar to that identified in people with MS (Koseoglu et al. 2006), and PD (Sathyaprabha et al. 2005). Physiological reasons for a decrease in strength may be related to atrophy due to the presence of mutant Huntingtin in skeletal muscle (Ciammola et al. 2011; She et al. 2011) and/or weight loss (Aziz and Roos 2013). Biomechanically, evidence of decreased postural control in people with HD (Brožová et al. 2011) may disrupt the normal synchrony of respiratory and postural muscles (Bianchi and Gestreau 2009) influencing force production. Physical inactivity (Busse et al. 2009; Quinn et al. 2013) and deconditioning may lead to decreased peripheral muscle strength (Busse et al. 2008) which is related to respiratory muscle strength (Buchman et al. 2008a).

Progressive decline in lung volume as described for type 1 hypoxaemic respiratory failure may lead to an increase in elastic load on the respiratory pump. Resistive load may be increased by incoordinated contraction of the valve muscles of the larynx and pharynx, dysfunction of which are noted in studies of swallow in people with HD (Heemskerk and Roos 2011; Kagel and Leopold 1992). Upper airway obstruction has been demonstrated in

people with PD (Buyse 2006; Sathyaprabha et al. 2005) who have similar swallow problems as people with HD.

This conceptual framework suggests that respiratory function may be impaired in people with HD and that this may lead to type 1 hypoxaemic and type 2 hypercapnic respiratory failure. Respiratory function in people with HD may be a delicate balance of altered central respiratory drive, decreased respiratory muscle capacity and an increased elastic and resistive load.

Figure 7 **Conceptual framework of type 1 hypoxaemic respiratory failure in people with Huntington's disease**

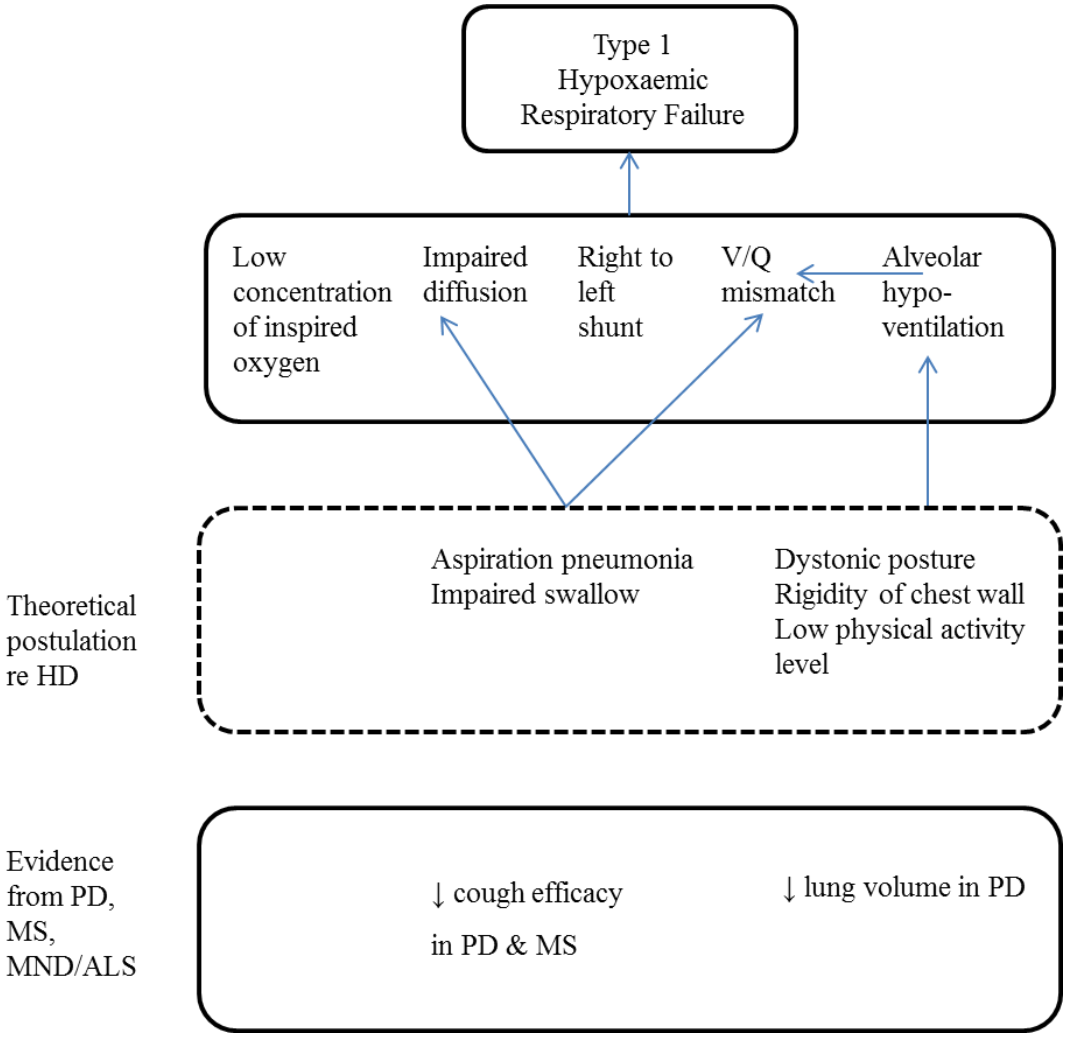
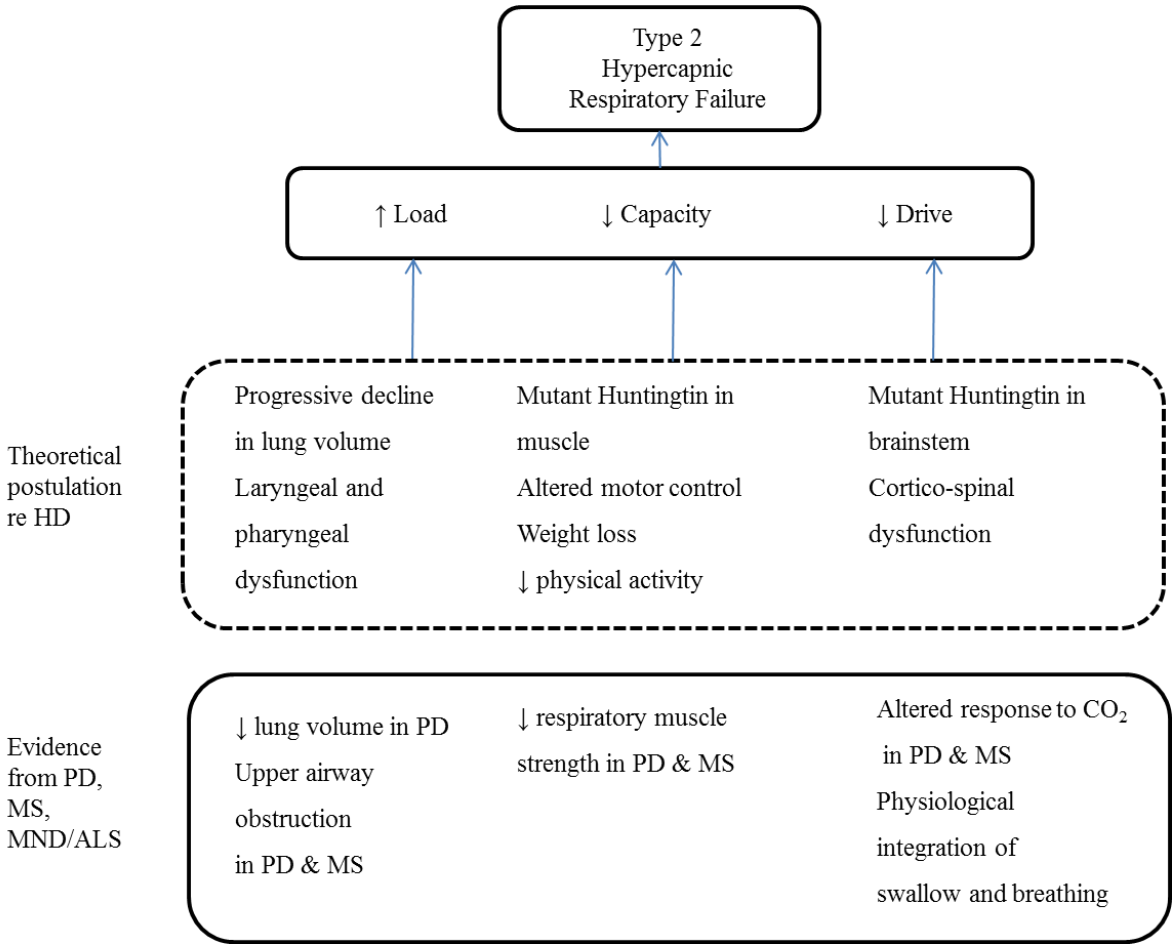


Figure 8 **Conceptual framework of type 2 hypercapnic respiratory failure in people with HD**



3.5 Observation study objectives

Chapters 2 and 3 have explored the pathological and functional changes resulting from the presence of mutant Huntingtin in people with Huntington's disease with specific reference to aspects that may impact on respiratory function and respiratory failure. The underlying causes of respiratory failure, type 1 hypoxaemic and type 2 hypercapnic, have also been explored in order to develop a conceptual framework for respiratory failure in people with HD. This framework provides theoretical assumptions and specific direction for an observational study exploring respiratory function in people with HD. In order to test the framework, it was necessary to compare respiratory function in people with HD with matched healthy control subjects; to use measures of disease progression to examine changes throughout the condition and to explore relationships with factors that may influence or be influenced by respiratory function. The objectives of the study were therefore to:

- investigate respiratory function in people with Huntington's disease and compare with healthy control subjects;
- investigate respiratory function throughout the progression of the disease;
- investigate factors that may influence and be influenced by respiratory function in people with Huntington's disease.

The principle research questions were:

- Is there a difference in respiratory function between healthy controls and people with Huntington's disease
- Does respiratory function change as Huntington's disease progresses?

Further research questions were:
If there is a difference in respiratory function between healthy controls and people with Huntington's disease:

- Is respiratory function related to swallow capacity?
- Is respiratory function related to posture?
- Is respiratory function related to exercise capacity?
- Is respiratory function related to physical activity?

The null hypotheses for the study were:

H_{01} There is no difference in respiratory function in people with HD compared to healthy control subjects;

H_{02} Respiratory function in people with HD does not change as the disease progresses;

H_{03} Respiratory function does not decrease over time;

H_{04} Respiratory function is not related to exercise capacity in people with HD;

H_{05} Respiratory function is not related to physical activity in people with HD;

H_{06} Respiratory function is not related to posture in people with HD;

H_{07} Respiratory function is not related to swallow capacity in people with HD;

4 Observation study methods

4.1 Research design and outcome measures

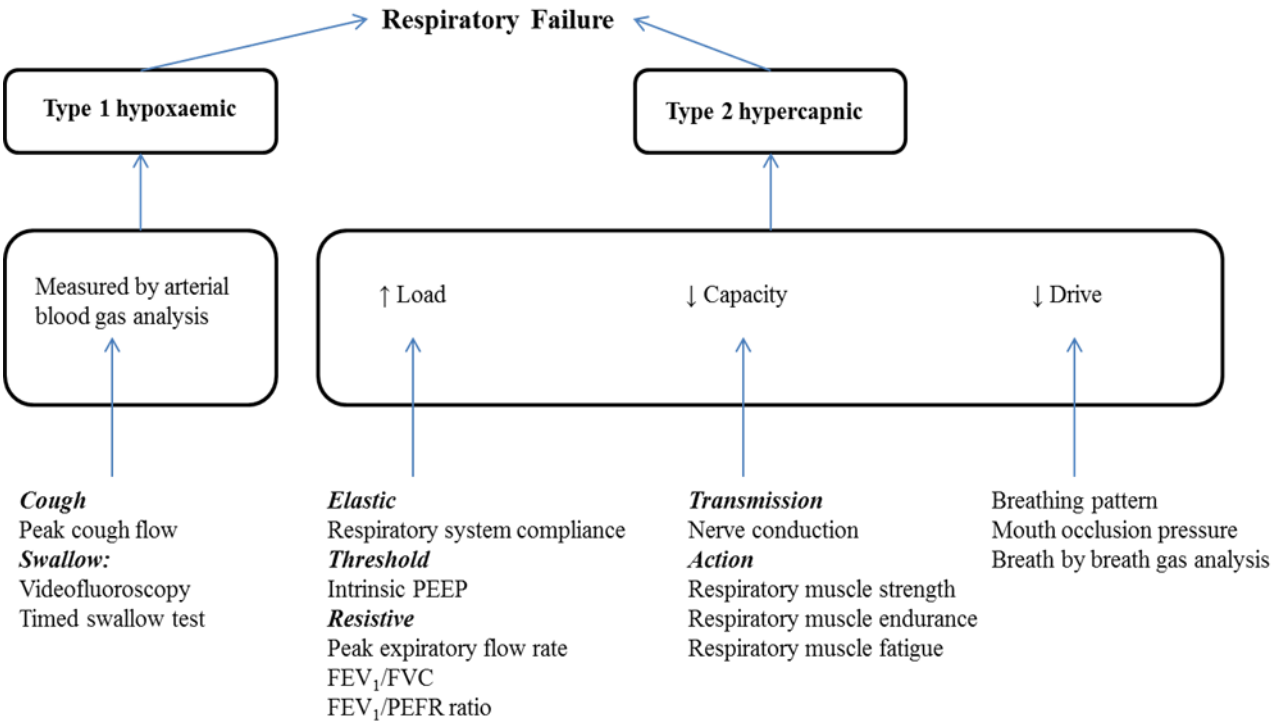
Observational studies may use one of three main research methods: Case control, cohort or cross sectional study. A case control study selects people with a particular condition (cases) and people without the condition (controls) and explores, retrospectively, both groups' exposure to a potentially contributing factor. The control group must be appropriately matched and there must be reliable evidence of exposure. A cohort study identifies firstly whether people have been exposed or not exposed to a factor and then gathers information from over a time scale to ascertain whether the exposure influences the pathological condition. The collection of data may be prospective or retrospective (Carlson and Morrison 2009). These two types of observational study are predominantly used to assess association between exposure and outcomes over time within a real world setting. Cross sectional studies are primarily used to determine prevalence of cases within a population at a given point in time but can also be used to infer causation. The advantages of this type of study are that data is collected only once and multiple outcomes can be assessed (Mann 2003). A prospective longitudinal study for this study was not appropriate as the length of time of observation may be between 40 and 50 years, from diagnosis of being gene positive to onset of symptoms and then to death. A retrospective study would be limited by the quality of evidence related to respiratory function that could be gathered. A cross sectional method was chosen as data could be collected from people with HD across the spectrum of the condition i.e. from pre-manifest to late stage and that multiple variables could be measured.

This observational study collected data from people who were gene positive and categorised as pre-manifest; people who were categorised as manifest HD and healthy participants. The categorisation of pre-manifest and manifest was based on the UHDRS:TMS and diagnostic confidence score of the consultant neurologist as described in section 2.4.

Comparisons of respiratory function were made between people with HD and healthy subjects to determine if respiratory function was different in people with HD. Respiratory function through the progression of the disease was investigated through correlation between measures of disease severity and respiratory function. To investigate influencing factors, correlations were carried out between measures of respiratory function and swallow capacity, posture, exercise capacity and physical activity.

Using the framework of respiratory failure as described in Chapter 3, respiratory function was categorised into measurable component parts, see Figure 9. Measurement of each component of the framework was discussed in Chapter 3.

Figure 9 Measurement of respiratory function



4.2 Measurement related to type 1 respiratory failure

Measures of saturation of oxygen were taken as an alternative to invasive arterial blood gas analysis as although it is susceptible to light and movement artefacts (Tremper 1989) it does provide an accurate representation of arterial blood gas (Decker et al. 1989). The measurements used were those taken before the six minute walk test. Variables that could influence type 1 respiratory failure were measured: cough and swallow efficacy. Cough efficacy was measured as voluntary cough using peak cough flow (PCF) as recommended by Bott et al. (2009). Assessment of swallow by subjective means and/or videofluoroscopy would require specialist training and therefore it was decided to measure swallow capacity using the timed swallow as it has been found to be reliable and valid in people with neurological conditions (Nathadwarawala et al. 1992).

In order to gain information on signs and symptoms related to respiratory and swallow dysfunction, a questionnaire was used. The questions relating to respiratory dysfunction were taken from the Royal Brompton Hospital Respiratory Muscle Symptom Score (Hart and Polkey 2001) and the swallow component was based on Hughes and Wiles (1996).

4.3 Measurement related to type 2 respiratory failure

Symptoms related to type 2 hypercapnic respiratory failure were collected via Royal Brompton Hospital Respiratory Muscle Symptom Score (Hart and Polkey 2001) with oxygen saturation and dyspnoea (Modified Borg Dyspnoea Scale) measured at the beginning of the six minute walk test. Capacity of the respiratory pump was measured by inspiratory and expiratory muscle strength and single breath work capacity. Volitional methods were chosen for respiratory muscle strength, including oral and nasal measures of inspiratory muscle strength, specific guidelines having been devised for these measures (American Thoracic Society/European Respiratory Society. 2002). Severe diaphragm weakness can be assessed by comparing FVC in supine and seated positions, with the former being 5-10% of the latter in normal subjects with abnormal values being >30% (American Thoracic Society/European Respiratory Society. 2002).

As the study design involved collecting a large number of variables both of respiratory function and influencing factors, it was felt that using a method that required subjects working to fatigue was not feasible for assessing respiratory muscle endurance. The alternative measure of single breath work capacity was used; although this has not been used in people with neurodegenerative conditions it is reliable in people with CF (Enright et al. 2006b)

Resistive load offered by lower and upper airways was measured as PEFR, FEV_1 and FEV_1/PEFR values following guidelines (Miller et al. 2005). Flow volume curves were also analysed using descriptors specified by Watson et al. (2009). Specific expertise and equipment to measure elastic load in terms of respiratory system compliance was not available to the researcher. As decreased lung volume results in decreased alveolar compliance (Dargaville et al. 2010), FVC was used as an indirect measure of elastic load. There was insufficient evidence that threshold load would be increased in people with HD and it was not measured.

There was insufficient evidence regarding central respiratory drive in people with HD and it was decided that the study be limited to measures of capacity and load; respiratory drive was not measured.

4.4 Variables influencing respiratory function

Swallow was measured using the timed swallow test as described by Hughes and Wiles (1996). Assessing posture using radiographic imaging was not feasible for this study and therefore measurement using photographic images was chosen as it is deemed reliable and valid in healthy subjects (van Niekerk et al. 2008). It was decided to use a bespoke software package to analyse thoracic angle, head tilt and neck angle as unpublished data within the researchers department indicated good reliability. In order to confirm this, further reliability studies were undertaken with healthy subjects and people with HD, see Appendix 1.

Measurement of exercise capacity using $\dot{V}O_{2max}$ was not undertaken due to lack of appropriate equipment. Exercise capacity was measured by the six minute walk test due to simplicity of the task and reliability in people with HD (Quinn et al. 2013).

Assessment of physical activity can be carried out objectively via activity monitors or subjectively via questionnaires. A disadvantage of activity monitors is the lack of specificity of task and therefore a questionnaire was used: the International Physical Activity Questionnaire (IPAQ). This questionnaire was found to be reliable and valid across 12 countries (Craig et al. 2003); in a meta-analysis (Ainsworth et al. 2012), and reliable specifically in people with HD (Quinn et al. 2013).

4.5 Pilot study

Five participants took part in a pilot study. The aim of the pilot was to:

- Familiarise the researcher with the protocol;
- Determine time necessary for data collection;

- Identify any issues with equipment;
- Identify any issues with standard operating procedures.

The outcomes of the pilot study were:

- Data collection would take approximately 1 hour 30 minutes;
- Spare batteries needed to be available for relevant equipment;
- DeVilbiss RT2 for assessment of SMIP did not always complete data collection and therefore its position was raised to ensure a wider reception width;
- A flange was necessary for maximal expiratory pressure manoeuvre;
- Explicit demonstrations and explanations were needed for respiratory manoeuvres.

4.6 Participants

4.6.1 Inclusion criteria: people with HD

As this was an observational study, few exclusion criteria were applied.

(i) Confirmed diagnosis of HD by neurologist;
(ii) Aged 18 years and older;
(iii) Able to understand instructions in English.

4.6.2 Exclusion criteria: people with HD

(i) Other health issues that would impact on the interpretation of data, these participants were excluded. Examples were previous cerebro vascular accident, severe chronic obstructive pulmonary disease and on-going treatment for cancer.
(ii) Participants were excluded if they were currently or had been involved in other research studies in the past two months.

4.6.3 Inclusion criteria: healthy controls participants

Healthy control participants were matched with people with HD for age, gender, body mass index and smoker/non-smoker matched individuals and must have been able to understand instructions in English.

4.6.4 Recruitment

Potential participants attending their routine clinic appointment were approached by Professor Anne Rosser, the clinician responsible for their care, and were invited to participate in the programme alongside the ‘Registry’ study, see Figure 10 and Figure 11. The clinics were associated with the Cardiff Huntington’s Disease Centre. Many patients attending the

HD clinic are already enrolled in the 'Registry' study (Ethic committee number: 04//WSE05/89). One of the optional components within the 'Registry' project includes permission to be contacted between visits. Patients who had consented to this component were contacted by letter and informed of the study. The researcher assumed responsibility for any further telephone follow up of the postal information sheet.

Participants recruited in this group ranged from people who were diagnosed with HD and had no symptoms through to those at the late stage of the disease.

Potential healthy control participants were recruited in one of three ways:

- From carers, friends or relatives of people with HD introduced by the patient and in the same manner as the participants with HD;
- From staff and students from Cardiff University;
- By individual recruitment by the researcher.

Twenty healthy control participants were recruited by an MSc student under the supervision of the researcher. All potential participants received an information sheet and were given at least one week to consider the information, before being contacted to discuss their involvement.

A pragmatic approach to the number of participants recruited to study was taken. The number was sufficient to include a range of disease severity from those with no symptoms to those at the late stage of the disease, within the context of number of patients attending the HD clinic.

Figure 10 Recruitment of participants with Huntington's disease

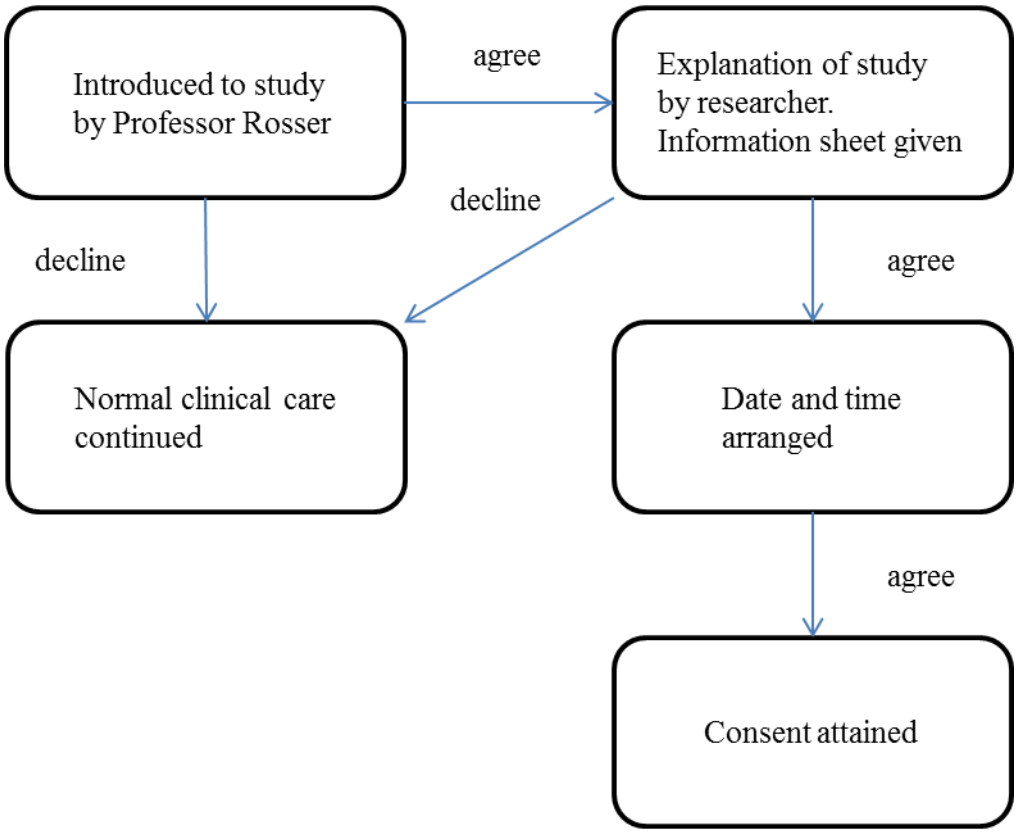
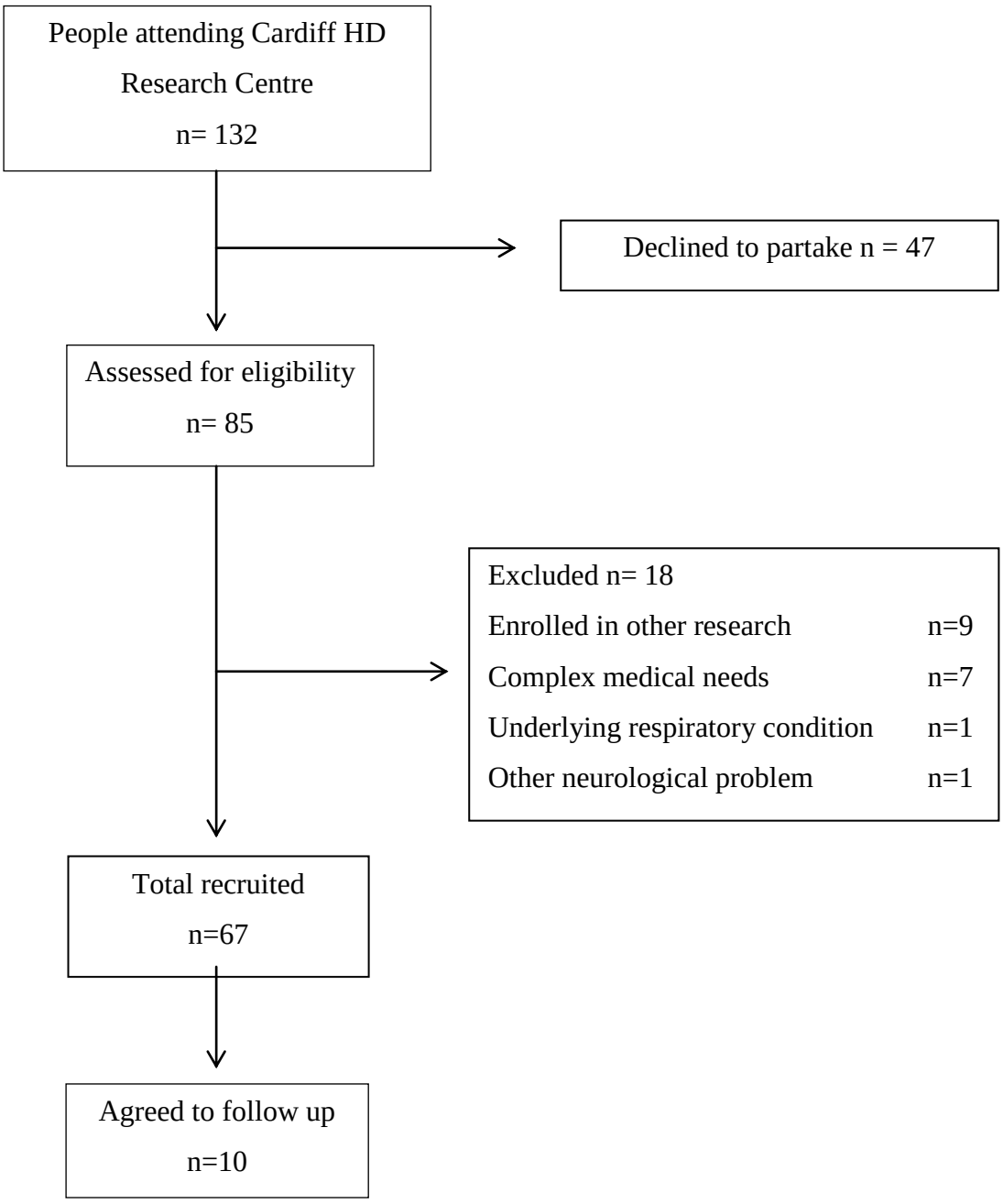


Figure 11 Observation study recruitment flow diagram



4.7 Observation study protocol

Participants in the observational study attended a data collection session that lasted between 90-120 minutes. This took place either at Cardiff University or the participants' homes. Data collection followed a similar format for each participant to minimise changing position, and provide breaks from the respiratory function tests. Respiratory function data were collected from 10 participants approximately one year after their initial assessment to explore change of respiratory function over time. The protocol for the assessment visit was as follows:

- Welcome, time for questions related to information sheet, consent gained
- Respiratory history – including respiratory symptoms
- Swallow history
- Measurement of height and weight
- Measurement of body mass index and FVC in supine
- Measurement of lung function in sitting: FEV_1, FVC, FEV_1/FVC, PEFR, PCF
- Physical activity questionnaire
- Measurement of respiratory muscle strength and endurance: MIP, MEP, SNIP, SMIP
- Swallow test
- Analysis of posture
- Six minute walk test including O_2 saturation and dyspnoea
- Barthel index

4.7.1 Demographic data

Age was determined from asking the patient and checking with their date of birth. Height and weight were measured using Seca height and weight scales. In order for the results to be compared with other studies in people with neurodegenerative conditions, the Barthel index was used to assess functional ability. The index is found in Appendix 3 and was completed by asking the participant and/or the carer the questions.

4.7.2 Measures of disease severity

Measures of disease severity were accessed via the participant's clinic notes. These included: UHDRS: TFC, TMS, functional and independence scores. Related measures such as cognitive scores were also accessed via the participant's clinic notes, see Appendix 3 for details of assessment scoring proforma. Categorisation of people with HD into pre-manifest and manifest was based on a clinical diagnosis as described in section 2.4.

4.7.3 Body mass index

Malnutrition influences both skeletal and respiratory muscles with diaphragm weight loss being proportional to that of skeletal muscle (Polla et al. 2004) and related to decreasing inspiratory muscle strength (Rochester and Esau 1984). Body mass index was therefore a potential confounder in this study and was measured using the bioelectrical impedance method in order to match people with HD and healthy control subjects.

Body mass index was measured using the Maltron Body Composition Analyser, see Appendix 4 for details. The participant was asked to lie flat on a bed or plinth, dependent upon data collection site. The sensors were placed on the right hand and foot. The hand sensors were placed just proximal to the third metacarpal phalangeal joint and the crease of the wrist. The foot sensors were placed just proximal to the second and third metatarsal joint and the crease of the ankle in line with the tibia, see Figure 12 for details.

Figure 12 Placement of sensors for body composition analysis

Cables were attached to the sensors, the black cable being the more distal attachment, on both hand and foot. The participant was asked to relax as much as possible during the test. Once data were inputted into the analyser, the test took approximately 10 seconds.

4.7.4 Respiratory history and swallow questionnaire

In order to gain further information relating respiratory function and swallow, a questionnaire was used to collect data from a daily living perspective. The respiratory history was based on the Royal Brompton Hospital Respiratory Muscle Symptom Score (Hart and Polkey 2001) and the swallow component was based on Wiles and Hughes (1996). The respiratory history and swallow questionnaire can be found in Appendix 3.

4.7.5 Respiratory function

4.7.5.1 Spirometry: FVC (sitting and supine), FEV_1, PEFR, Peak Cough Flow, Flow volume loops

Lung volumes and flows were measured using the Micromedical Microloop Spirometer with a bacterial filter, see Appendix 4 for details and Figure 13 and Figure 14 for images. All measurements, except FVC supine, were taken with the subject in an upright position sitting in a supported chair. The measurement techniques were explained and the participant practised the manoeuvres. Some subjects needed very simple instructions with visual cues in order to carry out the test appropriately, due to co-ordination problems. A forced expiratory manoeuvre was performed following American Thoracic Society guidelines (Miller et al. 2005), see Appendix 3. A flanged mouthpiece was used if necessary. The American Thoracic Society guidelines state that encouragement should be given during the test; however it was found that this was distracting for people with HD and therefore no encouragement was given to any subject.

Figure 13 The Micromedical Microloop Spirometer

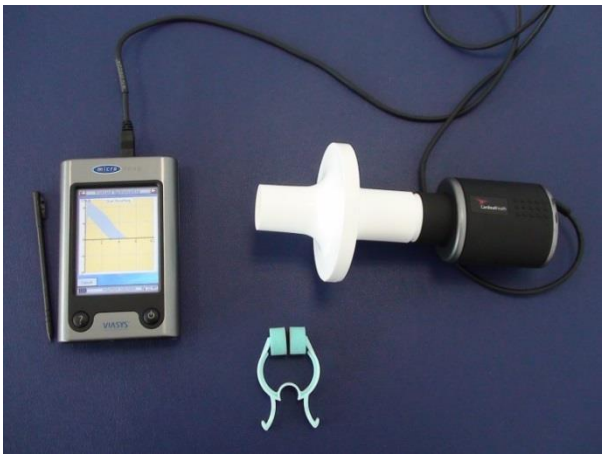


Figure 14 Using the Microloop Spirometer

4.7.6 Assessment of respiratory muscles

4.7.6.1 Respiratory muscle strength (MIP, MEP, SNIP)

Respiratory muscle strength was measured using the Micromedical MicroRPM, details are found in Appendix 4; see also Figure 15 and Figure 16. The measurement techniques were explained and the participant practised the manoeuvres. MIP was measured from residual volume, MEP from total lung capacity and SNIP from functional residual capacity following American Thoracic Society/European Respiratory Society guidelines (American Thoracic Society/European Respiratory Society. 2002), see Appendix 3. A flanged mouthpiece was used for oral tests if necessary. The best of a minimum of 10 sniff manoeuvres were taken for SNIP (Lofaso et al. 2006).

Figure 15 The Micromedical MicroRPM

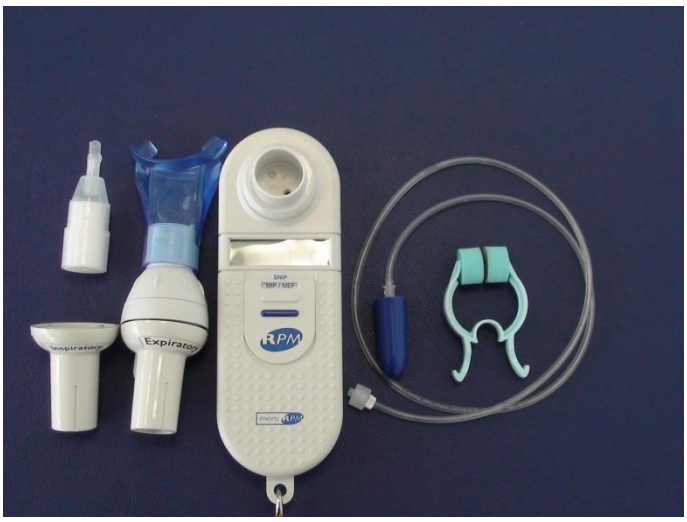
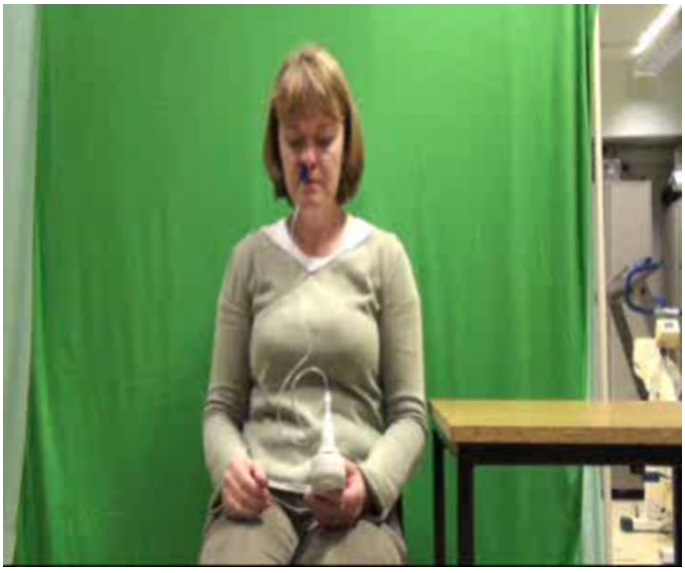


Figure 16 Using the Micromedical MicroRPM



4.7.6.2 Single-breath work capacity (SMIP)

Sustained maximal inspiratory pressure (SMIP) was measured using the DeVilbiss RT2 trainer, see Appendix 4 for details, see also Figures17-19. Testing was carried out using the method of Chatham et al (1999), see Appendix 3. A flanged mouthpiece was used if necessary. The measurement technique was explained and the participant practised the manoeuvres. Each manoeuvre went from residual volume and was sustained through to total lung capacity. The best of three sustained maximal inspiratory manoeuvres was used.

Figure 17 The DeVilbiss RT2

Figure 18 Using the DeVilbiss RT2

Figure 19 Measuring SMIP using DeVilbiss RT2

4.7.7 Exercise Tolerance

Exercise tolerance was assessed by the 6 minute walk test, and carried out in accordance with American Thoracic Society guidelines (American Thoracic Society. 2002), on a 20 metre lap rather than a 100 metre lap. The total distance covered was the number of laps times 20 plus any portion of a lap as measured by a trundle wheel. If the participant stopped walking during the test and needed a rest, they were told to rest and then continue walking when they felt able. The timer was not stopped. If the participant could not continue or the researcher felt that they should not continue, the participant was returned to their chair. The distance covered, the time stopped and the reason for stopping was recorded. Predicted values were based on Enright and Sherrill (1998). Measures of O_2 saturation, heart rate, respiratory rate, dyspnoea using the Modified Borg Dyspnoea Scale (Borg 1970), see Appendix 3 and perceived exertion using the Borg Perceived Exertion Scale (Borg 1982) see Appendix 3 were taken before and after the six minute walk test.

4.7.8 Physical Activity

Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) (IPAQ Research Committee. 2005), see Appendix 3 for details. This was completed by the researcher asking the participant the questions and prompting if necessary.

4.7.9 Posture

Posture was assessed by digital analysis as per protocol in the reliability study, see Appendix 1. Video recordings were made of the subject sitting at a self-selected comfortable upright position; images were extracted from the video recording and processed using a bespoke Matlab programme.

4.7.10 Swallow Capacity

The swallow capacity test was carried out according to the instructions of Hughes and Wiles (1996). Competency of cough was assessed by the researcher prior to this test. If the participant was being fed through a percutaneous endoscopic gastrostomy tube or did not have a competent cough, this measure was not taken. An amount of water was measured into a clear plastic drinking cup. A spout or straw was used when necessary. The amount was 150ml if the participant had no swallow problems, 50ml if there were swallow problems (personal communication Dr T Hughes March 2009). The participant was asked to drink the water as quickly as possible. The time taken between the bolus of water reaching the lips and the end of the last swallow was taken. The number of swallows was also counted. The volume of water swallowed, the time to complete the drink, and the number of swallows was recorded. Predicted values were based on Hughes and Wiles (1996).

4.8 Data analysis

4.8.1 Analysis of normality of data

Data were assessed for normality through histograms, Shapiro-Wilk test and Q-Q plots. Frequency histograms were analysed visually to assess the frequency curve with a normal distribution curve (Portney and Watkins 2009). A normal Q-Q plot demonstrates a straight diagonal line of expected values with a plot of the observed values closely following the line. Deviation from normality is noted if the plot of observed points deviates from the diagonal line (Field 2009). The Shapiro-Wilk test assess whether the observed distribution deviates from a normal distribution by comparing the scores in the sample to a normally distributed set of scores with the same mean and standard deviation. If the result is significant i.e. $p<0.05$, the observed data are different to the normally distributed data and is therefore classed as non-normal (Field 2009).

4.8.2 Descriptive data analysis

Data were analysed descriptively by means, standard deviations and 95% confidence intervals [CI]. Graphically, box plots were used to describe central tendency and spread of data and scatterplots were used to illustrate potential relationships between variables. Flow-volume loops were analysed based on descriptors from (Watson et al. 2009) and (Pellegrino et al. 2005)

4.8.3 Inferential analysis

The choice of inferential analysis was based on the outcome of assessment of normality, with non-parametric tests being chosen if normality was not evident in the data. Between group differences i.e. between people with pre-manifest HD, people with manifest HD and healthy control could be analysed using a one way ANOVA or Kruskal-Wallis test as the non-parametric equivalent. Post-hoc analysis for Kruskal-Wallis is the Mann-Whitney U test with Bonferroni correction as multiple comparisons are carried out (Portney and Watkins 2009). Relational analysis was carried out using Pearson correlation coefficient or the non-parametric equivalent Spearman rank correlation coefficient. Relationships were described using the following descriptors (Portney and Watkins 2009):

0.00< r >0.25	little/no relationship
0.25< r >0.50	fair relationship
0.50< r >0.75	moderate to good relationship
r >0.75	good to excellent relationship

4.9 General ethical considerations

All work undertaken as part of this study complied with the Research Governance Framework for Health and Social Care in Wales and the Cardiff University Research Governance Framework. All participant identification and referral procedures as well as procedures for data storage, processing and management complied with the Data Protection Act 1998.

Ethical approval was gained from the Research Ethics Committee for Wales (08/MRE/65); Cardiff and Vale University Health Board gave research and development approval (08/IBD/4316) and Cardiff University acted as sponsor (SPON 579-08), see Appendix 2. The researcher complied with the School of Healthcare Sciences lone working policy when carrying out home visits. The researcher met the participants at the Cardiff Huntington's disease research and management clinic and arrangements made for the home visit. The

researcher kept in contact with a member of staff from Cardiff University at the beginning and end of each visit and carried a mobile phone throughout the visit.
Data were stored confidentially on password protected computers maintained on the Cardiff University Network. Files were only accessible to the researcher responsible for the running of the study and the supervisors. All paper records were stored in a locked filing cabinet, with keys available only to researcher. All essential documents generated by the study were kept in the study master file. All conversations that took place during the interviews were audio recorded for the purposes of analysis. All audio and video records obtained were stored in locked cabinets in the School of Healthcare Sciences, Cardiff University. All personal data of participants were destroyed at the end of the study and all other data will be kept in locked storage for 15 years in accordance with the Cardiff University Research Governance Framework.

4.10 Specific ethical considerations

4.10.1 Risk during assessment

All participants were fully informed of testing procedures before participation, and made aware that they could withdraw from the study without reason at any time. Participants were carefully monitored during testing by the researcher who was experienced in lung function testing and clinical assessment. The care and comfort of the participants was ensured at all times.

4.10.2 Participants unable to consent

The aim of the observational study was to investigate respiratory function at different stages of HD and it was essential to include people with HD at all stages of the disease. HD, as a chronic degenerative disease, results in a progressive decline in mental ability and some people with HD did not have the capacity to make decisions about their participation in the study. The researcher, in discussion with clinician responsible for their care, decided whether potential participants had the capacity to give consent. The decision was based on a 2 stage test, based on the Mental Capacity Act 2005, code of practice (Department for Constitutional Affairs. 2007):

Stage 1

- Did the participant have an impairment of or a disturbance in the function of their mind or brain?
- Did the impairment/disturbance mean that the person is unable to make a specific

decision when they used to?

Stage 2

The decision as to whether a person was able/unable to make a decision was based on:

- whether the person understood the information related to the decision;
- whether the person could retain that information;
- whether the person could use or weigh that information or;
- whether the person could communicate his/her decision.

If it was deemed that the person was unable to decide to give consent, a nominated consultee was approached to decide whether the person would participate in the research.

4.10.3 Identification of a respiratory problem

During assessment of respiratory function, participants may have been identified as having a specific respiratory problem. If this was the case, Dr Hope-Gill, consultant physician at Llandough Hospital had agreed to clinically screen the participant. No participants were identified as having a respiratory problem during data collection.

4.10.4 Possible aspiration following swallow test

Participants were monitored during and after the swallow tests for possible aspiration. Suction apparatus was available throughout testing and the researcher was competent in its use.

4.10.5 Increased burden on participants

The main burden for participants participating in this research was their time. For the observational study participants gave up approximately two hours of their time for data collection.

4.10.6 Increased anxiety during/post data collection

Potential increased anxiety during or after data collection was minimised by a supportive and empathetic approach being used throughout data collection. Full contact details of the researcher were given to participants at the end of the study.

4.10.7 Project management

The project was primarily managed through the supervisory team of Dr Enright and Professor Busse who have specialist knowledge in inspiratory muscle training and HD respectively. The team met monthly for updates and discussion. Professor Rosser was also available to

oversee the project with opportunities for discussion at the weekly HD research and management clinic.

4.10.8 User involvement

The development of this study was based on discussions within the European Huntington's Disease Network Physiotherapy Working group and the Regional Care Advisor from the U.K. Huntington's Disease Association. On-going discussions took place with members of the Wales Huntington's Disease Involving People group, throughout the study.

5 Observational study results

5.1 Recruitment

People with HD were recruited from clinics organised through the Cardiff Huntington's Disease Research Centre, at which approximately 170 patients attend. Potential participants were informed of the study by the clinician responsible for their care and further details were provided by the researcher. Those participants who were willing to take part in the study were contacted to arrange a date and time for the assessment; recruitment took place over three years. In total 132 people were approached see Figure 11. 67 consented to the study (people with pre-manifest HD=20, people with manifest HD=47), 47 refused or did not reply, 18 were unsuitable. Reasons for unsuitability were: participant in other trials (n=9); chronic obstructive pulmonary disease (n=1); concurrent neurological problem (n=1); complex medical needs (n=7). In the people with manifest HD group, 7 were early stage, 22 middle stage and 18 late stage as determined by their TFC scores.

Healthy control participants (n=39) were recruited from a number of sources. Relatives and carers were approached as were staff and students of Cardiff University. Toward the end of the recruitment stage, specific recruitment was targeted to males who smoked and were aged over 45 years in order to match the people with HD group.

5.1.1 Potential confounding factors

Demographic data regarding gender, age, body mass index, fat free mass and smoking habit are displayed in Table 3. There were no statistically significant differences between the groups in gender (χ^2 =1.44, p=0.488, standardised residuals -0.6 to 0.6). The manifest group were significantly older than healthy control and people with pre-manifest HD, as would be expected. The age of the people with pre-manifest HD group (42.80 ±12.04) reflects the age of onset of clinical symptoms (Kelly et al. 2009). The difference in age between the groups could influence the findings as respiratory muscle strength and lung volumes alter with age (Lalley 2013; Polla et al. 2004) and for that reason, predicted values for respiratory function were used when possible.

People with pre-manifest HD had a higher body mass index (BMI) than those with people with manifest HD, although there was no difference between healthy control and people with pre-manifest HD or healthy control and people with manifest HD. These can be classified as healthy control (26.52 ±6.38) and people with pre-manifest HD (28.39 ±6.34) being 'pre-obese' and people with manifest HD (23.99 ±3.70) as 'normal' according to the World Health Organisation classification of BMI (World Health Organisation. 2006). In this study

therefore, people with manifest HD had normal BMI with people with pre-manifest HD being toward the upper end of pre-obese and healthy control being at the lower end of pre-obese. This difference in BMI was not reflected in fat free mass (FFM), with no significant difference across the groups. The lack of statistical difference in FFM across the groups excludes it as a confounding variable in this study.

Although there were significantly more non-smokers in the healthy control group (χ^2 =13.17, exact p=0.01, standardised residual=1.7), there was no significant difference in pack years across the groups (Kruskall-Wallis χ^2 =2.12, p=0.347). Pack year is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. For example, one pack year is equal to smoking one pack (20 cigarettes) per day for one year (Prignot 1987). Pack years for smokers and ex-smokers was 18.75 ±10.7 (healthy control); 14.77 ±11.14 (people with pre-manifest HD); 22.80 ±16.92 (people with manifest HD).

Table 3 Demographic data for people with HD and healthy control subjects

	Healthy control n=39		**Pre-manifest HD n=20**		**Manifest HD n=47**	
	Male	Female	Male	Female	Male	Female
Gender	18	21	9	11	27	20
Age (years) mean ± sd [CI]	46.74 ±15.81 [41.62,51.87]		42.80 ±12.04 [37.16,48.44]		53.28 ±12.98 [49.46,57.09]	
Body Mass Index Kg/m^2 mean ± sd [CI]	26.52 ± 6.38 [24.45,28.59]		28.39 ± 6.34 [25.23,31.54]		23.99 ± 3.70 [22.90,25.09]	
Fat free mass (%) mean ± sd [CI]	66.80 ±13.60 [62.39,71.21]		65.66 ±12.73 [59.70,71.62]		67.97 ±11.73 [63.94,72.00]	
Smoker	5		8		12	
Ex-smoker	3		5		11	
Non-smoker	31		7		24	

The groups of healthy control, people with pre-manifest HD and people with manifest HD were matched for all confounding variables, except for age and therefore it was necessary to undertake analysis of respiratory function as % predicted values as well as absolute values.

5.1.2 Measurements of Huntington's disease and functional ability

The scores for Unified Huntington's Disease Rating Scale: Total Motor Score (UHDRS: TMS); Total Functional Capacity (TFC); functional assessment and independence are shown in Table 4. People with HD were categorised as pre-manifest and manifest based on a clinical diagnosis as described in section 2.4.

Table 4 Measurement of severity of Huntington's disease

	Pre-manifest HD		Manifest HD	
	Mean ±sd	**Range**	**Mean ±sd**	**Range**
UHDRS:TMS (0-124)	n=16 3.94 ±4.53	0-15	n=46 58.75 ±24.00	4-100
TFC (0-13)	n/a all 13		n=47 4.72 ±4.04	0-12
Functional Assessment. (0-25)	n/a all 25		n=43 11.63 ±8.60	0-25
Independence (0-100%)	n/a all 100%		n=40 59.88 ±25.98	0-100

UHDRS:TMS Unified Huntington's Disease Rating Scale: Total Motor Score
TFC Total Functional Capacity

There was some overlap in UHDRS:TMS scores between people with pre-manifest HD and people with manifest HD groups, which indicates that although motor impairment was noted in some people with pre-manifest HD they were not showing signs unequivocal of HD. All people with pre-manifest HD were functionally able and independent as noted by TFC, functional assessment, independence scale. The pragmatic approach to recruitment ensured that the full range of scores was observed in TFC, functional assessment, and independence in people with HD. The mean TFC score of 4.72, with 11 subjects having a score of 0, indicates that the sample was skewed toward less functionally able. The relatively large standard deviations and full range of scores indicate that although the sample may be skewed, the full range of severity of HD was included.

Functional ability was measured using the Barthel index. The mean scores for people with pre-manifest HD (n=20) and people with manifest HD group (n=47) were 99.75 ±1.12, range 95-100 and 62.45 ±39.53, range 0-100 respectively.

5.2 Normality of data

Data were assessed for normality using normal distribution histograms, Q-Q plots, Shapiro-Wilk values and the Levene statistic, see Appendix 5 for details. All variables demonstrated at least one element of non-normal distribution and therefore inferential analysis was carried out using non-parametric tests.

5.3 Data related to type 1 respiratory failure

5.3.1 Respiratory symptoms in people with Huntington's disease

A small proportion of people with HD attended their GP with breathing problems in the last year (pre-manifest HD=2 (10%), manifest HD=11(23.4%)), see Table 5. The reasons for GP visits in the two subjects with pre-manifest HD were asthma check-ups. The reasons given for going to the GP in people with manifest HD were: aspiration and chest infection (n=5); chest infection (n=3); anaphylaxis (n=1), breathlessness (n=1), rhinitis (n=1). Breathing problems that did not necessitate a GP visit were: Chesty/chest infection (n=2); cough/cold (n=2); persistent cough (n=1); aspiration (n=1); flu (n=1); difficulty breathing during eating (n=1); chest tightness (n=1); asthma (n=1); breathlessness (n=1); always bubbly (n=1). Those visiting the GP for chest infections had a TFC range of 0-5, indicating increased incidence of clinical respiratory problems later in disease progression. There did not appear to be any sub-clinical respiratory problems, as it was the same participants who did attend their GP who also had problems for which they did not seek GP advice. Almost half of those with manifest HD obtained flu vaccinations in order to reduce the likelihood of a severe respiratory infection.

Table 5 Respiratory symptoms in people with Huntington's disease

	Pre-manifest HD n=20			**Manifest HD n=47**		
	Yes n (%)	**No n (%)**	**Sometimes n (%)**	**Yes n (%)**	**No n (%)**	**Sometimes n (%)**
Have you been to the GP with breathing problems in the last year?	2 (10%)	18 (90%)	0 (0%)	11 (23.4%)	36 (76.6%)	0 (0%)
Have you had breathing problems that you didn't go to the GP about?	0 (0%)	19 (95%)	1 (5%)	7 (14.9%)	36 (76.6%)	4 (8.5%)
Have you had a flu vaccination in the last year?	7 (35%)	13 (65%)	0 (0%)	21 (47.7%)	23 (52.3%)	0 (0%)

5.3.2 Respiratory signs in people with Huntington's disease

Measures of heart rate, respiratory rate and O_2 saturation for both groups of people with HD were within normal ranges (Broad et al. 2012; Kispert 1987), see Table 6. This data suggests that the subjects completing this study did not have signs of acute respiratory problems.

Table 6 Respiratory signs in people with Huntington's disease

	Heart rate (beats per minute)	Respiratory rate (breaths per minute)	O_2 Saturation (%)
Pre-manifest HD	66 ± 11 n=18	18 ± 4 n=13	98 ± 1 n=17
Manifest HD	74 ± 12 n=34	15 ± 5 n=29	96 ± 2 n=33
Normal values	60-100 (Broad et al. 2012)	10-20 (Kispert 1987)	95-100 (Broad et al. 2012)

5.3.3 Swallow data

In people with manifest HD, 34 (63.9%) reported swallow problems, seven of which had a percutaneous endoscopic gastrostomy (PEG) tube fitted. One person with pre-manifest HD reported swallow problems. The qualitative data presented in Table 7 refers to all people with HD, except those with a PEG fitted. The majority (> 60%) of people with manifest HD reported problems in that they needed to be careful eating and that this required them to avoid certain foods and have other foods specially prepared. The majority (67.5%) also reported coughing and food 'going down the wrong way' when eating. Half of people with manifest HD used the compensatory technique of drinking water when eating and only 40% had difficulties keeping food in their mouth.

Table 8 provides quantitative data on swallow ability. Predicted values and 95% predicted lower value for swallow capacity and volume per swallow were calculated using data from Hughes and Wiles (1996). Swallow was categorised as normal/abnormal if the participant's absolute score was above/below the predicted 95% lower limit for that individual. Prediction equations were obtained from Wiles (2013).

In the pre-manifest group, one person stated that they had a swallow problem, yet the swallow capacity and volume per swallow were normal. In the manifest group, 6 people who stated they had no problem with swallow had abnormally low swallow capacity. Excluding those people (n=7) with a PEG tube, 32 people with manifest HD had abnormally low swallow capacity: 15 had a normal volume per swallow indicating that the problem was slow time for swallow; 17 had abnormal volume per swallow which could indicate either a volume or volume and timing problem.

Table 7 Swallow symptoms in people with Huntington's disease

	Pre-manifest HD n=20			Manifest HD n=40		
	Yes n (%)	**No n (%)**	**Sometimes n (%)**	**Yes n (%)**	**No n (%)**	**Sometimes n (%)**
Do you need to be careful when eating?	1 (5%)	19 (95%)	0 (0%)	24 (52.2%)	12 (26.1%)	4 (10.0%)
Do you need to avoid certain foods?	0 (0%)	20 (100%)	0 (0%)	19 (47.5%)	16 (40.0%)	5 (12.5%)
Does your food need to be specially prepared?	0 (0%)	20 (100%)	0 (0%)	21 (52.5%)	14 (35.0%)	5 (12.5%)
Do you have difficulties keeping food in your mouth?	0 (0%)	20 (100%)	0 (0%)	9 (22.5%)	24 (60.0%)	7 17.5%)
Do you need to drink water when you are eating?	0 (0%)	20 (100%)	0 (0%)	14 (35.0%)	20 (50.0%)	6 (15.0%)
Do you cough when you are eating?	0 (0%)	18 (90%)	2 (10%)	11 (27.5%)	13 (32.5%)	16 (40.0%)
Does food go down the wrong way when you are eating?	0 (0%)	18 (90%)	2 (10%)	7 (17.5%)	13 (32.5%)	20 (50.0%)
Do you get short of breath when you are eating?	0 (0%)	19 (95%)	1 (5%)	1 (2.5%)	35 (87.5%)	4 (10.0%)

Table 8 Quantitative swallow data in people with Huntington's disease

	Pre-manifest HD n=20	Manifest HD n=46
Normal swallow capacity (frequency)	20 (100%)	7 (15.2%)
Mean ±sd % predicted swallow capacity	127.32 ±68.89	28 ±34.35
Normal volume per swallow (frequency)	20 (100%)	22 (47.8%)
Mean ±sd % predicted volume per swallow	127.24 ±48.98	47.07 ±41.46

5.3.4 Cough efficacy

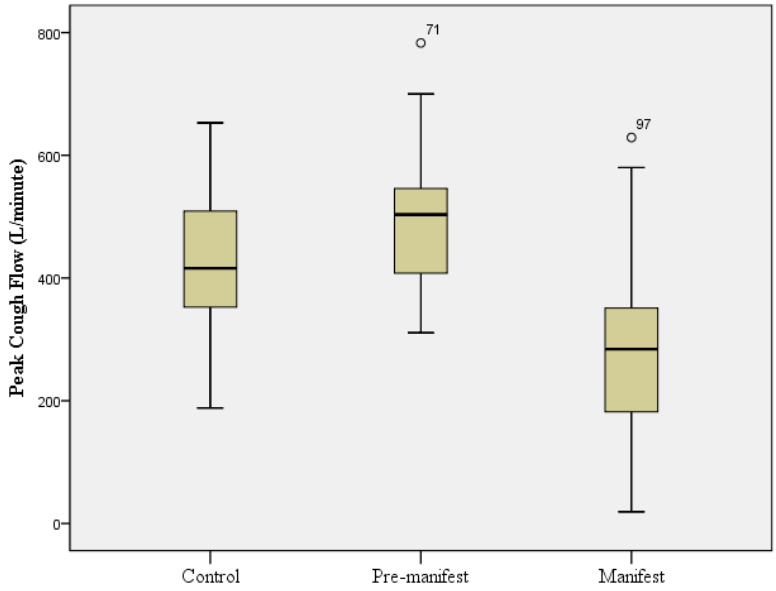
Cough efficacy was assessed by measuring PCF, see Table 9 and Figure 20, with comparisons being made between healthy control, people with pre-manifest HD and people with manifest HD. Mean PCF in people with manifest HD (269.46 L/min ±154.58) and a minimum value of 19 L/min indicating that some subjects had ineffective cough. The minimum value of 188L/min in the healthy control group required further analysis of the raw data, which identified two participants with PCF of < 270 L/min. One participant had a PCF of 265 L/min was aged 58, a non-smoker and normal values for FVC %predicted (99%), FEV_1% predicted (102%) and PEFR%predicted (90%). MEP %predicted was slightly low (73%) which may relate to the low PCF; the low result. The participant with PCF of 188L/min was aged 46, a non-smoker with normal FVC%predicted (91%) and slightly low FEV_1%predicted (86%), PEFR%predicted (68%) and MEP%predicted (74%). It is unclear why the PCF values were so low and they may be testing anomalies.

Analysis using Kruskall-Wallis demonstrated significant differences across the three groups in PCVF (χ^2 36.78, $p<0.001$). Mann-Whitney U with Bonferroni correction (significance level of $p\leq0.017$) analysis showed that PCF was significantly lower in people with manifest HD compared to healthy control ($U=289.00$, $p<0.001$) and people with pre-manifest HD ($U=86.00$, $p<0.001$); there was no difference between healthy control and people with pre-manifest HD ($U=262.00$, $p\leq0.04$), see Table 10.

Table 9 **Peak cough flow in healthy control and people with Huntington's disease**

	n	Peak Cough Flow (PCF) Litres/minute	
		Mean ±sd	Range
Healthy control	39	433.95 ±102.48	188.00–653.00
Pre-manifest HD	20	504.55 ±124.12	311.00–783.00
Manifest HD	47	269.46 ±154.58	19.00–629.00

Figure 20 **Box plot of peak cough flow (L/min) across groups**



Control	Healthy control participants
Pre-Manifest	People with pre-manifest HD
Manifest	People with manifest HD

Table 10 Post-hoc analysis for differences in peak cough flow across groups

	Mean difference [95% CI]	**Mann-Whitney U** P value
Healthy control and pre-manifest HD	-70.60 [131.27,-9.93]	262.00 0.040
Healthy control and manifest HD	164.49 [105.80,223.17]	289.00 <0.001
Pre-manifest HD and manifest HD	235.09 [155.70,314.48]	86.00 <0.001

Further analysis of data related to swallow capacity and cough efficacy indicate a significant relationship between these two variables, $r=0.515$, $p<0.001$.

The data related to type 1 respiratory failure shows that 23.4% of people with manifest HD reported respiratory problems and that these were predominantly people at the late stage of the disease. Underlying this data, 84.8% had abnormal swallow and 16.4% had ineffective cough (<160L/minute) with both variables having a positive relationship. This indicates that people with HD are at risk of aspiration pneumonia and type 1 respiratory failure.

5.4 Data related to type 2 respiratory failure

5.4.1 Capacity of respiratory pump

The capacity of the respiratory pump was measured via inspiratory and expiratory muscle strength and single breath work capacity. A comparison was made between FVC in supine and upright sitting in order to investigate severe diaphragm weakness. The objective data related to inspiratory muscle strength were supplemented by subjective data from the respiratory questionnaire.

5.4.1.1 Respiratory questionnaire

The Royal Brompton Respiratory muscle symptom score questionnaire (Hart and Polkey 2001) was used to collect data regarding respiratory symptoms. The questions related to inspiratory muscle weakness (question 1), nocturnal hypoventilation (questions 2-4) and expiratory muscle weakness (questions 5-6), see Table 11.

Table 11 Respiratory related problems in people with Huntington's disease

	Pre-manifest HD n=20			Manifest HD n=47		
	Yes n (%)	**No n (%)**	**Sometimes n (%)**	**Yes n (%)**	**No n (%)**	**Sometimes n (%)**
Do you ever feel breathless?	2 (10%)	10 (50%)	8 (40%)	6 (12.8%)	29 (61.7%)	12 (25.5%)
Do you get morning headaches? n=20; 45	3 (15%)	16 (80%)	1 (5%)	2 (4.4)	38 (84.4%)	5 (11.1%)
Do you feel sleepy during the day?	6 (30%)	6 (30%)	8 (40%)	14 (29.8%)	20 (42.6%)	13 (27.7%)
Do you have difficulties sleeping?	2 (10%)	11 (55%)	7 (35%)	12 (25.5%)	24 (51.1%)	11 (23.4%)
Do you have difficulties coughing?	0 (0%)	18 (90%)	2 (10%)	12 (25.5%)	29 (61.7%)	6 (12.8%)
Do you have difficulties clearing secretions?	0 (0%)	19 (95%)	1 (5%)	7 (14.9)	35 (74.5%)	5 (10.6%)

Breathlessness is a key symptom of inspiratory muscle weakness, and this was evident in 50% or less of people with HD. The reasons for becoming breathless were: walking hills (n=3); walking (n=2); sitting (n=2); panic (n=1). The reasons for sometimes becoming breathless were: walking uphill (n=6); walking (n=4); running (n=2); playing squash (n=2); chesty (n=1); agitated (n=1); sitting (n=1); lying flat (n=1); jogging (n=1); hay fever (n=1). The reasons for breathlessness tended to be on exertion e.g. walking uphill, walking or running, with only 3 people feeling breathless while at rest. The median score on the Modified Borg Dyspnoea Scale taken before the six minute walk test was 0 for both people with pre-manifest and manifest HD, indicating no breathlessness. The range of scores was 0-0.5 for people with pre-manifest HD and 0-2 for people with manifest HD, see Table 33. Expiratory muscle weakness was also noted by difficulties in coughing and/or clearing secretions. These difficulties were predominantly in people at the later stages of the disease, TFC 0-3 (n=8) but four people in the middle stage also experienced these difficulties. These difficulties were also reported by three people in people with pre-manifest HD.

5.4.1.2 Respiratory muscle strength and single breath work capacity

Data from respiratory muscle strength and single breath work capacity tests are shown in Table 12. There were no differences between values for healthy control and people with pre-manifest HD, people with manifest HD showed significantly reduced values compared to healthy control and people with pre-manifest HD values for respiratory muscle strength and single breath work capacity see Figure 21and Figure 22 and Tables 12-16.

Measurements were taken of FVC in supine and sitting in people with pre-manifest and manifest HD to identify if diaphragm weakness existed. In normal subjects FVCsupine is 5-10% of that in sitting, a decrease of >30% indicates severe weakness (American Thoracic Society/European Respiratory Society. 2002). FVCsupine was 96.03 ±7.34% (range 72.89-108.55) and 89.69 ±27.27% (range 0.00-128.57) of FVC sitting in people with pre-manifest HD and people with manifest HD respectively. Five individuals had FVCsupine <70% of FVC sitting. Three of these were late stage participants with FVC % predicted 8-22%; MIP 2-16% predicted and SNIP 2-37% predicted. Two were middle stage participants with FVC % predicted 61% and 73%; MIP 16-32% predicted and SNIP 37-5% predicted.

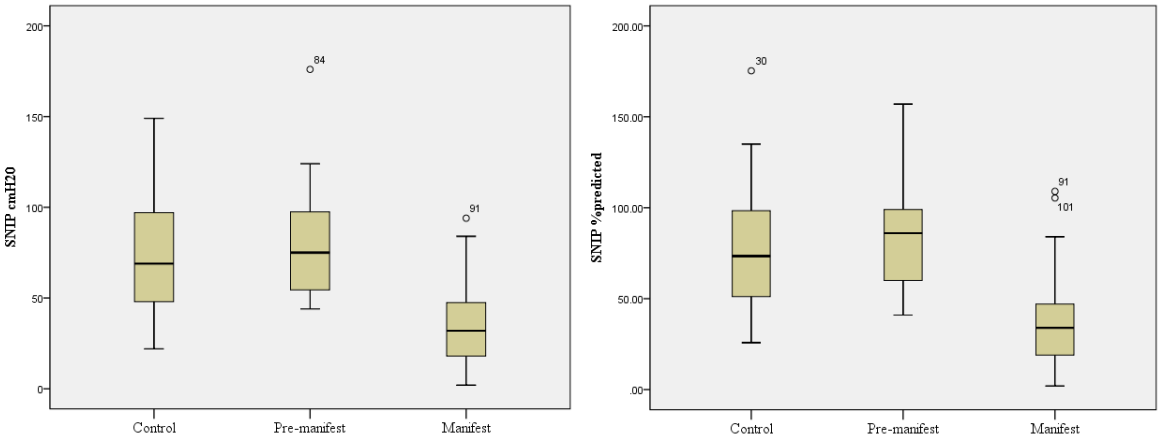
The data show generalised respiratory muscle weakness in people with manifest HD in inspiratory (MIP 29.31% predicted, SNIP 36.65% predicted) and expiratory muscles (29.06% predicted). SNIP values were less than MIP values in healthy control and people with pre-manifest HD, but not in people with manifest HD. This may be due to SNIP being relatively easier for people with HD to perform compared to MIP, with the sniff manoeuvre creating more complete neuromuscular activation (Fitting 2006). The recommendation that MIP and SNIP are not interchangeable (Uldry and Fitting 1995) is confirmed by the data in this study.

SMIP was significantly reduced in people with manifest HD (99.45 ±121.32) compared to healthy control (427.50 ± 221.52) and people with pre-manifest HD (519.68 ±272.51). Although normative values for SMIP have not been developed, data from healthy subjects in a respiratory muscle training intervention study had baseline SMIP values of 415 ±129 and 504 ±184 in both groups (Enright et al. 2006b). This would indicate that single breath work capacity in healthy control and people with pre-manifest HD may be typical values, whereas the values from people with manifest HD are atypical.

Table 12 Respiratory muscle function across groups

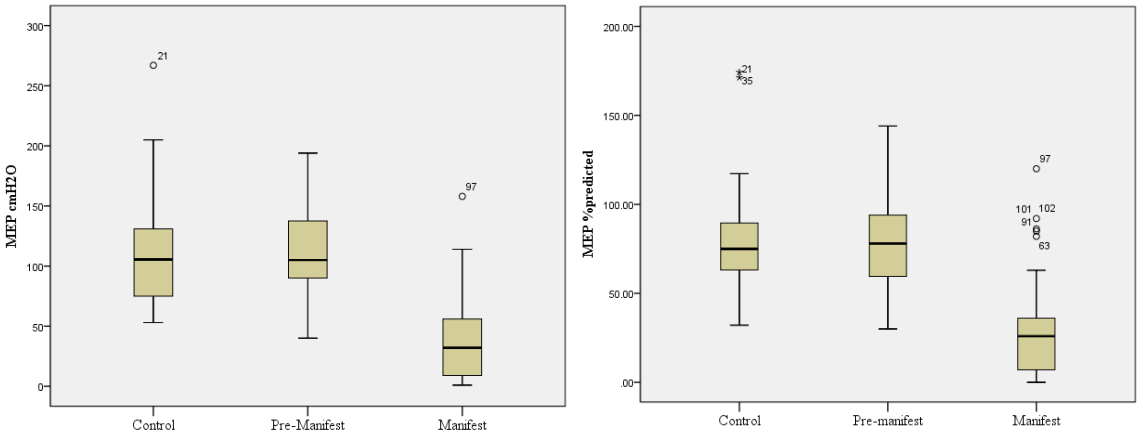
	n	Maximal Inspiratory Pressure (MIP) cmH_2O		% Predicted MIP	
		Mean ±sd	**Range**	**Mean ±sd**	**Range**
Healthy control	38	83.00 ±31.43	29–144	95.29 ±32.27	41.06–158.97
Pre-manifest HD	19	87.00 ±30.33	50–166	97.68 ±29.45	46.00–160.00
Manifest HD	46	25.60 ±21.49	0–94	29.31 ±24.25	0.00–121.00
		Sniff Nasal Inspiratory Pressure (SNIP) cmH_2O		**% predicted SNIP**	
		Mean ±sd	**Range**	**Mean ±sd**	**Range**
Healthy control	38	74.13 ±31.68	22–149	77.97 ±32.84	25.82–175.29
Pre-manifest HD	19	81.32 ±33.22	44–176	85.29 ±32.69	41.00–157.00
Manifest HD	42	34.79 ±23.79	2–94	36.65 ±26.62	2.00–109.00
		Maximal Expiratory Pressure (MEP) cmH_2O		**% predicted MEP**	
		Mean ±sd	**Range**	**Mean ±sd**	**Range**
Healthy control	38	108.89 ±42.88	53–267	79.03 ±29.79	32.07–174.25
Pre-manifest HD	19	112.21 ±37.73	40–194	80.67 ±31.40	30.00–144.00
Manifest HD	46	39.63 ±35.53	1–158	29.06 ±28.38	0.00–120.00
		Sustained Maximal Inspiratory Pressure (SMIP) pressure time unit			
		Mean ±sd		**Range**	
Healthy control	38	427.50 ±221.52		50–942	
Pre-manifest HD	19	519.68 ±272.51		220–1159	
Manifest HD	38	99.45 ±121.32		0–397	

Figure 21 Box plots of SNIP and SNIP% predicted across groups



a) SNIP across the three groups b) SNIP % predicted across the three groups

Figure 22 Box Plots for MEP and MEP% predicted across groups



a) MEP across the three groups b) MEP% predicted across the three groups

SNIP	Sniff Nasal Inspiratory pressure (cmH_2O)
MEP	Maximal Expiratory Pressure (cmH_2O)
Control	Healthy control participants
Pre-Manifest	People with Pre-manifest HD
Manifest	People with Manifest HD

Table 13 Main differences in respiratory muscle function across groups

	Chi-square	p value
MIP	60.55	<0.001
MIP% predicted	62.97	<0.001
SNIP	40.2	<0.001
SNIP% predicted	38.50	<0.001
MEP	52.50	<0.001
MEP% predicted	46.84	<0.001
SMIP	49.95	<0.001

control (n=39), pre-manifest (n=20), manifest groups (n=47), df=2.
Kruskall-Wallis analysis
MIP Maximal inspiratory pressure (cmH_2O)
SNIP Sniff nasal inspiratory pressure (cmH_2O)
MEP Maximal expiratory pressure (cmH_2O)
SMIP Sustained maximal inspiratory pressure (Pressure time unit)

Table 14 Post-hoc analysis of respiratory muscle function: control and pre-manifest groups

	Healthy control Mean ±sd	Pre-manifest HD Mean ±sd	Mean difference [95%CI]	U value p
MIP	83.00 ±31.43	87.00 ±30.33	-4.00 [-21.50,13.50]	345.00 0.786
MIP% predicted	95.28 ±32.27	97.68 ±29.24	-2.39 [-20.03,15.24]	356.00 0.953
SNIP	74.13 ±31.68	81.32 ±33.22	-7.18 [-25.31,10.94]	321.50 0.504
SNIP% predicted	77.97 ±32.84	85.29 ±32.69	-7.32 [-25.78,11.14]	320.00 0.488
MEP	108.89 ±42.88	112.21 ±37.73	-3.316 [-26.55,19.91]	326.00 0.553
MEP% predicted	79.03 ±29.79	80.67 ±31.40	-1.64 [-18.72,15.44]	348.00 0.826
SMIP	427.50 ±221.52	519.68 ±272.51	-92.18 [-226.99,42.62]	301.50 0.314

Mann-Whitney U analysis
MIP Maximal inspiratory pressure (cmH_2O)
SNIP Sniff nasal inspiratory pressure (cmH_2O)
MEP Maximal expiratory pressure (cmH_2O)
SMIP Sustained maximal inspiratory pressure (Pressure time unit)

Table 15 **Post-hoc analysis of respiratory muscle function: control and manifest groups**

	Healthy control **Mean ±sd**	**Manifest HD** **Mean ±sd**	**Mean difference [95%CI]**	**U value** **p**
MIP	83.00 ±31.43	25.60 ±21.41	57.40 [45.97,68.84]	112.00 <0.001
MIP% predicted	95.29 ±32.27	29.31 ±24.25	65.98 [53.70,78.26]	84.00 <0.001
SNIP	74.13 ±31.68	34.42 ±23.63	39.71 [27.44,51.99]	240.00 <0.001
SNIP% predicted	77.97 ±32.84	36.65 ±26.61	41.32 [28.07,54.58]	242.00 <0.001
MEP	108.89 ±42.88	38.87 ±35.52	70.02 [53.11,86.93]	163.50 <0.001
MEP% predicted	79.03 ±29.79	29.06 ±28.38	49.97 [37.31,62.62]	183.00 <0.001
SMIP	427.50 ±221.52	99.45 ±121.32	328.05 [246,409.69]	120.00 <0.001

Mann-Whitney U analysis
MIP Maximal inspiratory pressure (cmH_2O)
SNIP Sniff nasal inspiratory pressure (cmH_2O)
MEP Maximal expiratory pressure (cmH_2O)
SMIP Sustained maximal inspiratory pressure (Pressure time unit)

Table 16 Post-hoc analysis of respiratory muscle function: pre-manifest and manifest groups

	Pre-manifest HD Mean ±sd	Manifest HD Mean ±sd	Mean difference [95%CI]	U value p
MIP	87.00 ±30.33	25.60 ±21.41	61.40 [48.23,74.58]	37.00 <0.001
MIP% predicted	97.68 ±29.24	29.31 ±24.25	68.37 [54.33,82.42]	31.00 <0.001
SNIP	81.32 ±33.22	34.42 ±23.63	46.90 [32.09,61.70]	81.50 <0.001
SNIP% predicted	85.29 ±32.69	36.65 ±26.61	48.64 [32.82,64.47]	83.50 <0.001
MEP	112.21 ±37.73	38.87 ±35.52	73.34 [53.70,92.98]	68.50 <0.001
MEP% predicted	80.67 ±31.40	29.06 ±28.38	51.61 [35.65,67.56]	96.50 <0.001
SMIP	519.68 ±272.51	99.45 ±121.32	420.24 [316.10,524.38]	38.00 <0.001

Mann-Whitney U analysis
MIP Maximal inspiratory pressure (cmH_2O)
SNIP Sniff nasal inspiratory pressure (cmH_2O)
MEP Maximal expiratory pressure (cmH_2O)
SMIP Sustained maximal inspiratory pressure (Pressure time unit)

5.4.2 Load placed on the respiratory pump

FVC as a measure of lung volume was used as an indirect measure of elastic load. FEV_1/FVC is used as an indicator of obstructive and restrictive disorders. Resistive load created by lower and upper airways was measured as PEFR, FEV_1 and FEV_1/PEFR and visual analysis of flow-volume loops.

5.4.2.1 Elastic load

Data from lung function tests are shown in Table 17, with box plots illustrating differences across the groups in Figure 23, and statistical analysis in Tables 18-21. Measures of forced vital capacity (FVC) were greatly reduced in people with manifest HD; mean % predicted 56.70 ±31.69. Seven participants in the healthy control group had FVC%predicted <80%. Further analysis of the raw data did not highlight a respiratory problem in specific participants as each had normal values in other respiratory variables and therefore none of these participants were referred for further investigation. Participants with FVC%predicted (n=7) included 1 male, ranged from 21-83 years old, were all non-smokers had %predicted values for FEV_1 67-88%; PEFR 68-98% and MIP 44-138% with PCF values of 304-508L/min.

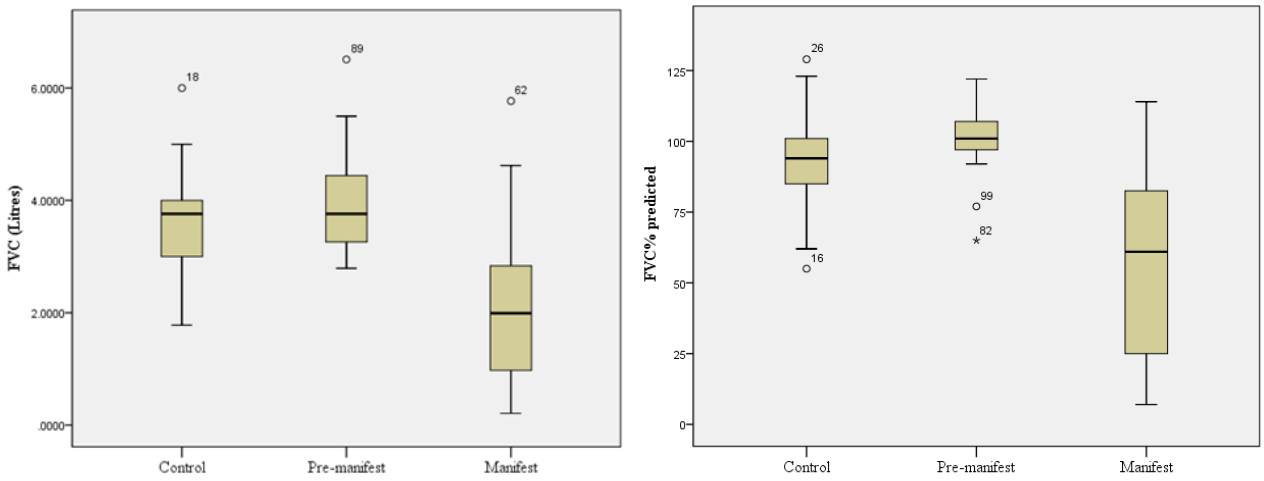
The variance in data from people with manifest HD data were greater than that in people with pre-manifest HD and healthy control groups, 13.84 and 15.89 respectively, demonstrating that people with manifest HD were less homogenous than people with pre-manifest HD or healthy control. This would be expected considering the range of disease severity and functional ability. For FVC% predicted, 36 people with manifest HD (53.73%), had a value of <80%, this being the critical value in people with ALS for exploring supportive non-invasive ventilation if respiratory symptoms also exist (Andersen et al. 2012). Of these 36 people, 18 were late, 17 middle and 1 early stage of the disease. FEV_1/FVC was higher in people with manifest HD (89.89 ±11.22) compared to healthy control (85.64 ±10.18) and people with pre-manifest HD (85.48 ±9.93). This difference was significant between the three groups, but when Bonferroni correction was applied for post-hoc analysis, the differences between healthy control and people with manifest HD and between people with pre-manifest HD and people with manifest HD were not significant. This indicates a restrictive pattern in people with manifest HD as defined as ≥70 and FVC <80%predicted (Ford et al. 2013). The significantly decreased lung volume and trend of increased FEV_1/FVC, suggests that elastic load is increased in people with manifest HD.

Table 17 Lung volume across groups

	N	Forced vital capacity (FVC) litres		%predicted FVC	
		Mean ±sd	Range	Mean ±sd	range
Healthy control	39	3.59 ±0.92	1.78–6.00	94.05 ±15.89	55–129
Pre-manifest HD	20	3.93 ±0.97	2.79–6.51	101.15 ±13.84	65–122
Manifest HD	47	2.14 ±1.39	0.21–5.77	56.70 ±31.69	7–114
		FEV_1/FVC			
		Mean ±sd		Range	
Healthy control	39	85.64 ±10.18		52.71–101.00	
Pre-manifest HD	20	85.48 ±9.93		64.82–114.00	
Manifest HD	47	89.89 ±11.22		62.88–119.05	

FEV_1/FVC Forced expiratory volume in 1 second/forced vital capacity

Figure 23 Box plots of FVC, FVC% predicted across groups



a) FVC in the three groups b) FVC% predicted in the three groups

FVC Forced vital capacity (litres)

Table 18 Main differences in lung volume across groups

	Chi-square	p value
FVC	33.71	<0.001
FVC% predicted	43.76	<0.001
FEV_1/FVC	6.27	0.036

control (n=39), pre-manifest (n=20), manifest groups (n=47), df = 2.

FVC Forced vital capacity (litres)

FEV_1/FVC Forced expiratory volume in 1 second/forced vital capacity

Table 19 Post-hoc analysis of lung volume: control and pre-manifest groups

	Healthy control Mean ±sd	Pre-manifest HD Mean ±sd	Mean difference [95%CI]	U value p
FVC (Litres)	3.59 ±0.92	3.93 ±0.97	-0.34 [-0.86,0.17]	331.00 0.342
FVC % predicted	94.05 ±15.89	101.15 ±13.83	-7.10 [-15.49,1.29]	263.50 0.043
FEV_1/FVC	85.64 ±10.18	85.48 ±9.93	0.15 [-5.41,5.71]	353.50 0.559

FVC Forced vital capacity (litres)
FEV1/FVC Forced expiratory volume in 1 second/forced vital capacity

Table 20 Post-hoc analysis of lung volume: control and manifest groups

	Healthy control Mean ±sd	Manifest HD Mean ±sd	Mean difference [95%CI]	U value p
FVC (Litres)	3.59 ±0.91	2.14 ±1.39	1.45 [0.93,1.96]	352.50 <0.001
FVC% predicted	94.05 ±15.89	56.70 ±31.69	37.35 [26.25,48.45]	285.50 <0.001
FEV_1/FVC	85.64 ±10.18	89.89 ±11.22	-4.26 [-8.89,0.38]	683.50 0.043

FVC Forced vital capacity (litres)
FEV1/FVC Forced expiratory volume in 1 second/forced vital capacity

Table 21 Post-hoc analysis of lung volume: pre-manifest and manifest groups

	Pre-manifest HD Mean ±sd	Manifest HD Mean ±sd	Mean difference [95%CI]	U value p
FVC (Litres)	3.93 ±0.97	2.14 ±1.39	1.79 [1.11,2.47]	131.00 <0.001
FVC% predicted	101.15 ±13.83	56.70 ±31.69	44.45 [29.68,59.21]	87.50 <0.001
FEV_1/FVC	85.48 ±9.93	89.89 ±11.22	-4.41 [-10.19,1.38]	308.50 0.027

FVC Forced vital capacity (litres)
FEV1/FVC Forced expiratory volume in 1 second/forced vital capacity

5.4.2.2 Resistive load

Large airway obstruction as measured by PEFR% predicted (49.49% ±29.53) in people with manifest HD was greater than small airway obstruction as measured by FEV_1, % predicted (60.51% ±33.94), see Table 22.

FEV_1 predicted was significantly less in people with manifest HD (60.51% ±33.94) compared to healthy control (95.26% ±14.88) and people with pre-manifest HD (101.35% ±15.19), see Tables 23-26. Although this would appear to indicate small airway obstruction, when these data are analysed alongside decreased lung volume, it may be due to a restrictive pattern rather than obstructive.

Five participants in the healthy control group had FEV_1%predicted < 80%. Three of these people also had FVC%predicted <80% indicating a restrictive respiratory pattern rather than obstructive due to airway narrowing. One participant, aged 49, with FEV_1%predicted 74% was a non-smoker with FVC%predicted 87%; PEFR%predicted 84% and MEP%predicted 70%. The low FEV_1%predicted value may highlight low effort during the test.

One participant, aged 30 with FEV_1%predicted 58% was a non-smoker with FVC%predicted 92%, PEFR%predicted 59% and MEP%predicted 87%. Data related to airway obstruction were low, but study notes did not highlight any respiratory problem.

Table 22 Resistive load across groups

	n	Forced expiratory volume in 1 second (FEV_1) litres		% predicted FEV_1	
		Mean ±sd	Range	Mean ±sd	range
Healthy control	39	3.02 ±0.83	1.64–5.00	95.26 ±14.88	58–129
Pre-manifest HD	20	3.31 ±0.79	2.16–4.86	101.35 ±15.19	57–121
Manifest HD	47	1.88 ±1.20	0.25–4.67	60.51 ±33.94	9–121
		Peak expiratory flow rate (PEFR) litres/minute		% predicted PEFR	
Healthy control	39	457.41 ±113.22	247–671	100.13 ±18.71	59–131
Pre-manifest HD	20	435.05 ±139.73	145–678	92.60 ±24.63	34–129
Manifest HD	47	221.49 ±141.61	32–581	49.49 ±29.53	6–115

Table 23 Main differences in resistive load across groups

	Chi-square	p value
FEV_1	28.09	<0.001
FEV_1% predicted	33.80	<0.001
PEFR	47.85	<0.001
PEFR% predicted	51.35	<0.001

control (n=39), pre-manifest (n=20) and manifest groups (n=47), df=2.
FEV_1 Forced expiratory volume in one second (litres)
PEFR Peak expiratory flow rate (litres/minute)

Table 24 Post-hoc analysis of resistive load: control and pre-manifest groups

	Healthy control Mean ±sd	Pre-manifest HD Mean ±sd	Mean difference [95%CI]	U value p
FEV_1	3.02 ±0.83	3.31 ±0.79	-0.29 [-0.74,0.16]	297.00 0.135
FEV_1% predicted	95.26 ±14.88	101.35 ±15.19	-6.09 [-14.34,2.16]	272.50 0.060
PEFR	457.41 ±113.22	435.05 ±139.73	22.36 [-45.21,89.93]	365.50 0.695
PEFR% predicted	100.13 ±18.71	92.60 ±24.63	7.58 [-3.97,19.02]	325.00 0.298

FEV_1 Forced expiratory volume in one second (litres)
PEFR Peak expiratory flow rate (litres/minute)

Table 25 Post-hoc analysis of resistive load: control and manifest groups

	Healthy control Mean ±sd	Manifest HD Mean ±sd	Mean difference [95%CI]	U value p
FEV_1	3.02 ±0.83	1.88 ±1.20	1.14 [0.69,1.59]	406.00 <0.001
FEV_1% predicted	95.26 ±14.88	60.51 ±33.94	34.75 [23.10,46.39]	360.50 <0.001
PEFR	457.41 ±113.224	221.49 ±141.61	235.92 [180.12,291.72]	180.50 <0.001
PEFR% predicted	100.13 ±18.71	49.49 ±29.53	50.64 [39.78,61.50]	144.00 <0.001

FEV_1 Forced expiratory volume in one second (litres)
PEFR Peak expiratory flow rate (litres/minute)

Table 26 Post-hoc analysis of resistive load: pre-manifest and manifest groups

	Pre-manifest HD Mean ±sd	Manifest HD Mean ±sd	Mean difference [95%CI]	U value p
FEV_1	3.31 ±0.79	1.88 ±1.20	1.43 [0.84,2.01]	165.50 <0.001
FEV_1% predicted	101.35 ±15.19	60.51 ±33.94	40.84 [25.00,56.68]	136.50 <0.001
PEFR	435.05 ±139.73	221.49 ±141.61	213.56 [138.35,288.77]	120.00 <0.001
PEFR% predicted	92.60 ±24.63	49.49 ±29.53	43.11 [28.08,58.14]	124.00 <0.001

FEV_1 Forced expiratory volume in one second (litres)
PEFR Peak expiratory flow rate (litres/minute)

Further analysis of these data, see Table 27, show that 50.7% of all participants had a FEV_1/PEFR ratio of >8, which may indicate an upper airway obstruction, with no difference between people with pre-manifest HD and people with manifest HD (χ^2=1.317, p=0.251). Increased resistive load in people with HD is therefore more likely to be from an upper airway obstruction i.e. pharynx and larynx than bronchial obstruction.

Table 27 FEV_1/PEFR ratio in people with Huntington's disease

	FEV_1/PEFR ratio ≤8	FEV_1/PEFR >8
Pre-manifest HD	12 (60.0%)	8 (40.0%)
Manifest	21 (44.7%)	26 (55.3%)
All people with HD	33 (49.3%)	34 (50.7%)

FEV_1 Forced expiratory volume in one second (litres)
PEFR Peak expiratory flow rate (litres/minute)

This was further explored by visual analysis of flow volume loops, see Figures24 - 29. Truncation of the loop and flattened inspiratory curves are suggestive of vocal cord dysfunction (Watson et al. 2009) and these were illustrated in both people with pre-manifest HD (8 (44%)) and manifest HD (22 (51%)). Caution must be taken with diagnoses from flow volume curves as they do not accurately predict pathology and subject's full effort is needed during the manoeuvre (Pellegrino et al. 2005).

Visual analysis of plots for people with pre-manifest HD (n=18), showed 9 (50%) normal; 7 (39%) with flattened inspiratory curves (indicative of laryngeal/pharyngeal obstruction); 1 (5.5%) truncated (indicative of vocal cord dysfunction) and 1 (5.5%) with rounded expiration (indicative of main bronchi obstruction). Figure 24 and Figure 25 illustrate normal and abnormal curves in people with pre-manifest HD.

Analysis of flow volume curves for people with manifest HD (n=43) showed 4 (9%) normal; 2 (5%) normal shape but with reduced flow rates; 18 (42%) truncated; 7 (16%) irregular; 6 (14%) rounded expiratory curve; 4 (9%) flattened inspiratory curve; 2 (5%) with flow and volume too small to analyse. Figures 26 - 29 illustrate the abnormal curves found in people with manifest HD.

Figure 24 Normal flow volume curve in participant with pre-manifest Huntington's disease

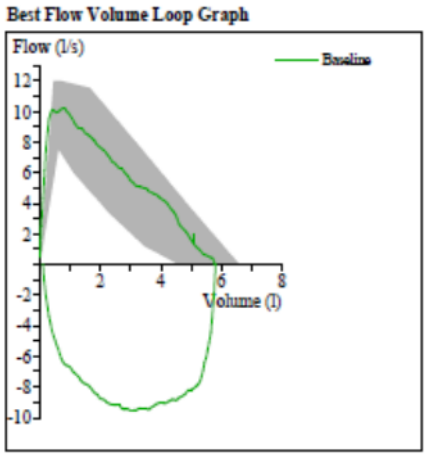
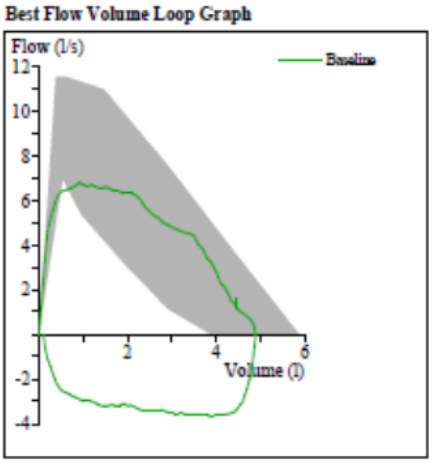
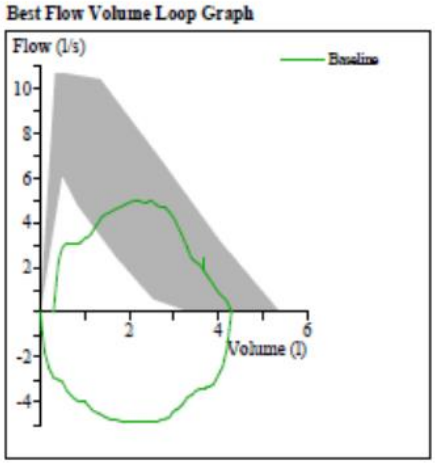


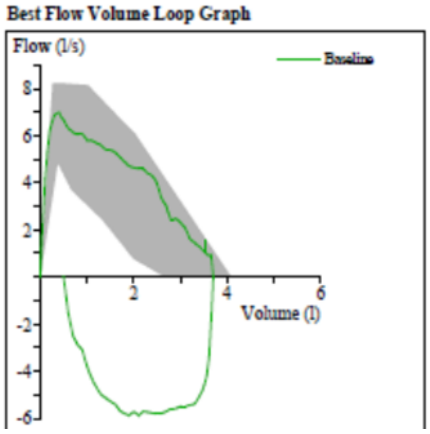
Figure 25 **Abnormal flow volume curves in people with pre-manifest Huntington's disease**



a) flattened inspiratory curve

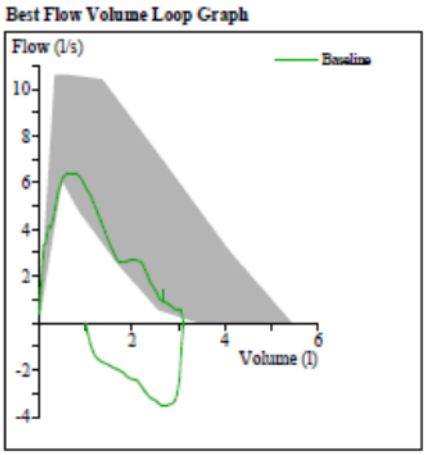


b) rounded expiration



c) truncated inspiratory curve

Figure 26 **Truncated flow volume curves in people with manifest Huntington's disease**



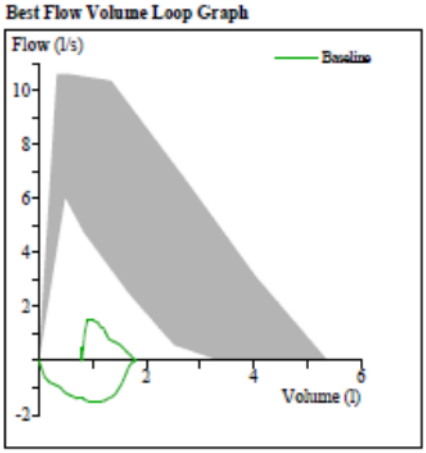


Figure 27 **Irregular flow volume curves in people with manifest Huntington's disease**

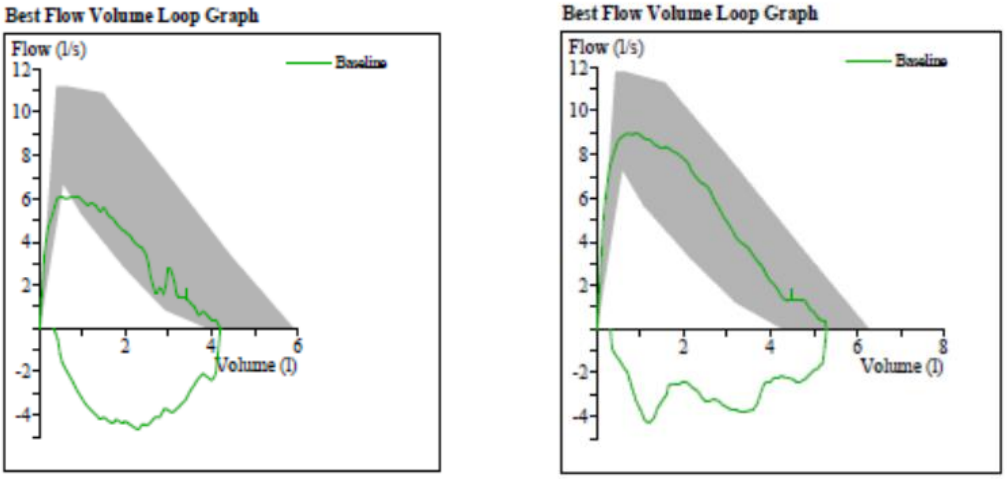


Figure 28 **Rounded flow volume curves in people with manifest Huntington's disease**

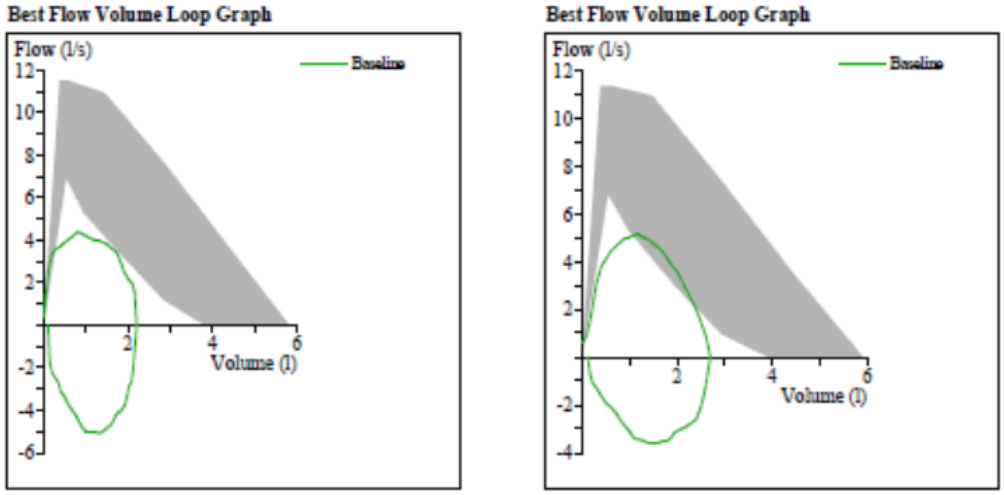
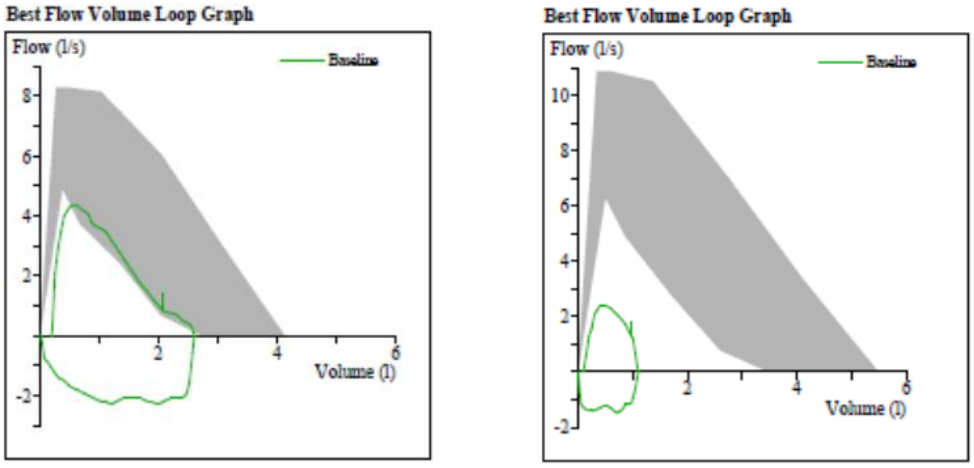


Figure 29 Flattened inspiratory curve in people with manifest Huntington's disease



The data collected indicate that both elastic and restrictive load may be increased in people with manifest HD. Decreased lung volume and the trend of a restrictive pattern suggest an increase in elastic load. Restrictive load is increased and appears likely to be due to upper airway obstruction (PEFR 49.49% predicted). Analysis of FEV_1/PEFR and flow volume loops suggest that restrictive load is increased in both people with pre-manifest and manifest HD, which may be due to laryngeal/pharyngeal dysfunction.

5.5 Variables influencing respiratory function

The relationships between respiratory function and variables that may influence or be influenced by respiratory function were explored in people with manifest HD. These variables were swallow, posture, exercise capacity and physical activity. Specific measures were chosen for each relational analysis, dependent upon the influencing variable.

The relationship between swallow capacity and respiratory function was explored using FVC, MIP, SNIP and MEP as lung volume, inspiratory and expiratory muscle strength are all components of effective cough (McCool 2006a). The relationship between PCF and swallow capacity has already been explored in section 5.3.4.

Altered thoracic posture may increase the load placed on the respiratory pump by decreasing lung volumes and altering the biomechanical properties of the respiratory muscles. Relationships between FVC, FEV_1/FVC, PCF, MIP and SNIP and thoracic angle were analysed.

Decreased exercise tolerance and physical activity may influence and be influenced by respiratory function. Decreased lung volume may decrease gaseous exchange with a

consequent decrease in exercise capacity. Decreased activity may cause general de-conditioning with loss of strength and endurance of muscles, both peripheral and respiratory. Decreased respiratory muscle strength, due to altered biomechanics and/or weakened muscles may lead to decreased activity. Relationships between exercise tolerance/physical activity and FVC, MIP, SNIP and SMIP were analysed.

5.5.1 Swallow capacity

Descriptive data regarding swallow capacity is in Table 8. Scatterplots of respiratory function and swallow capacity demonstrated positive relationships, see Figure 30. The relationships were significantly correlated: R_s ranged 0.515–0.781; R_s^2 ranged 0.265–0.610; $p<0.01$, see Figure 30 and Table 28. This analysis was repeated for % predicted swallow and respiratory function values see Table 29 with similar findings.

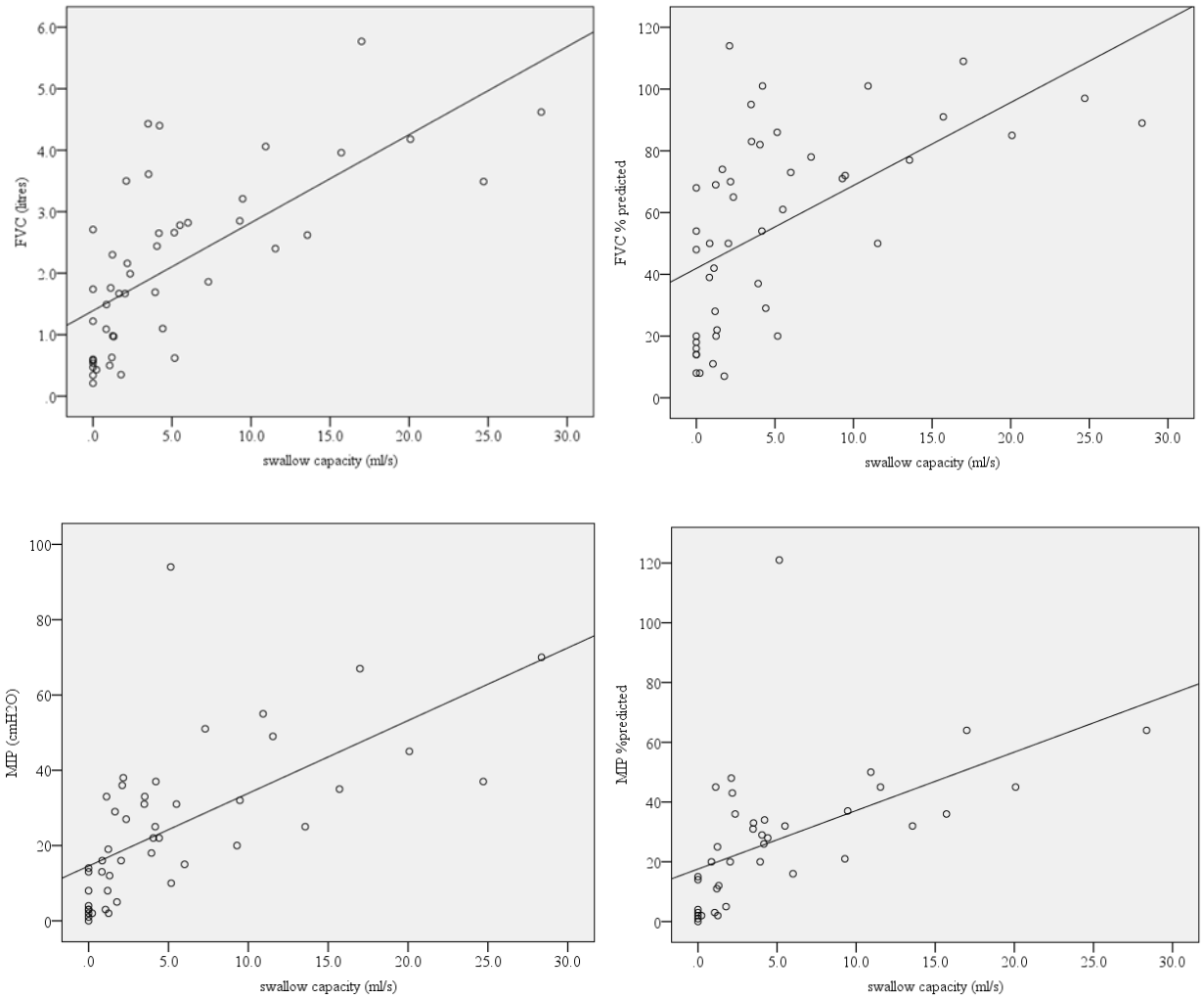
A significant positive relationship has already been established between swallow capacity and PCF, see section 5.3.4. Decreased swallow capacity is therefore related to low lung volume and hence increased load and decreased respiratory muscle strength and hence decreased capacity of the respiratory pump. These relationships were similar when absolute and predicted values were analysed.

Table 28 Relationships between respiratory function and swallow

	R_s	R_s^2	p value
MIP	0.781	0.610	<0.001
MIP% predicted	0.760	0.578	<0.001
FVC	0.741	0.549	<0.001
SNIP	0.705	0.497	<0.001
MEP	0.699	0.489	<0.001
FVC% predicted	0.690	0.476	<0.001
MEP% predicted	0.617	0.381	0.002
SNIP% predicted	0.597	0.356	<0.001
PCF	0.515	0.265	0.001

MIP Maximal inspiratory pressure (cmH_2O)
FVC Forced vital capacity (litres)
SNIP Sniff nasal inspiratory pressure (cmH_2O)
MEP Maximal expiratory pressure (cmH_2O)
PCF Peak cough flow (litres/minute)
R_s Spearman's correlation coefficient

Figure 30 Scatterplots of respiratory function against swallow capacity



MIP Maximal inspiratory pressure
FVC Forced vital capacity

Table 29 Relationships between % predicted respiratory function and %predicted swallow capacity

	R_s	R_s^2	p value
MIP% predicted	0.789	0.623	<0.001
FVC% predicted	0.705	0.497	<0.001
SNIP% predicted	0.681	0.464	<0.001
MEP% predicted	0.661	0.437	<0.001

MIP Maximal inspiratory pressure
FVC Forced vital capacity
SNIP Sniff nasal inspiratory pressure
MEP Maximal expiratory pressure
R_s Spearman's correlation coefficient

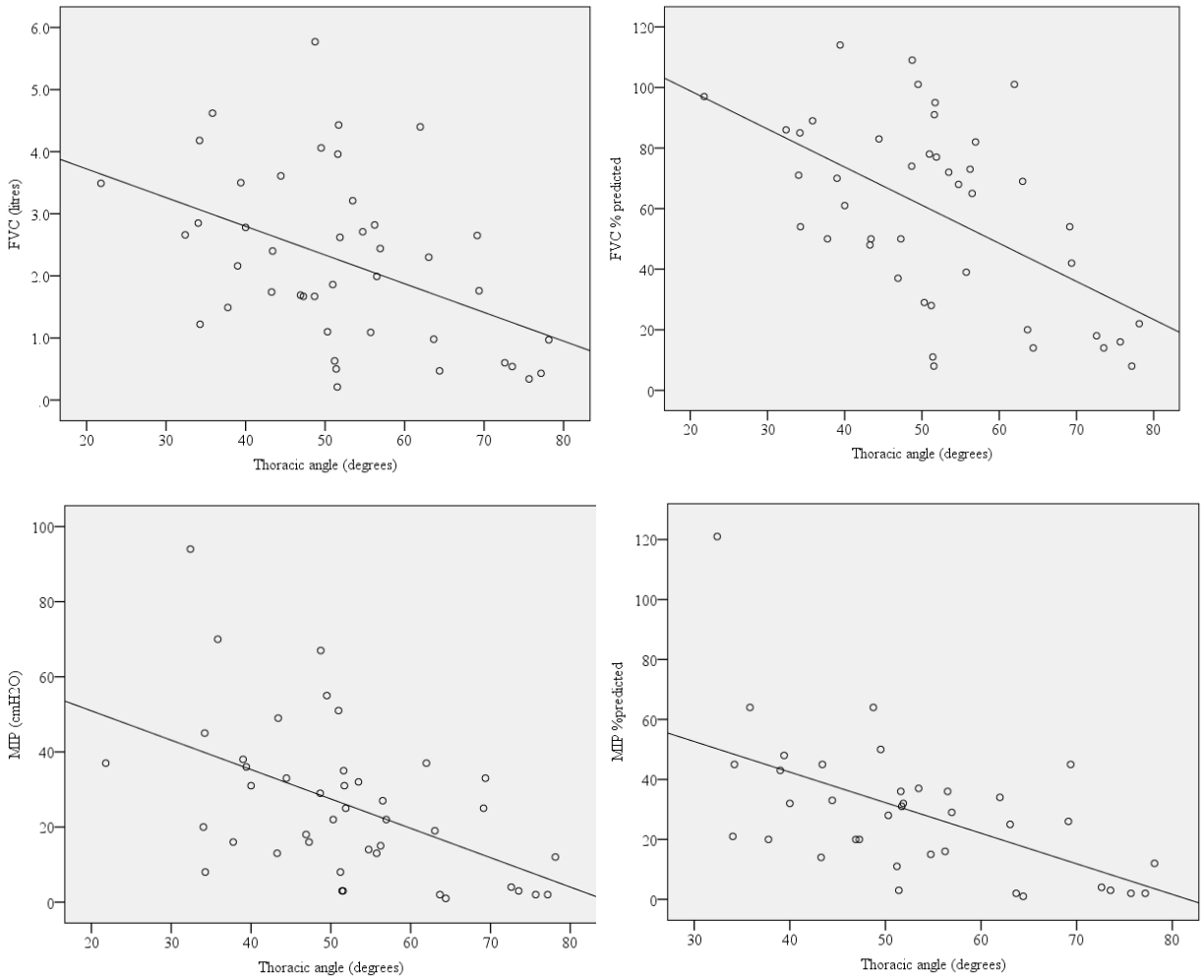
5.5.2 Posture

Descriptive data for thoracic, neck and head posture are detailed in Table 30. People with manifest HD were more kyphotic and had increased head tilt in comparison with people with pre-manifest HD. Analysis of respiratory function and posture was limited to thoracic angle. Scatterplots of respiratory function and thoracic angle demonstrated negative relationships, i.e. as thoracic angle increased, respiratory function decreased, see Figure 31. The relationships were significantly correlated, except for FEV_1/FVC: R_s ranged -0.388-0.551; R_s^2 ranged 0.151-0.304; $p < 0.05$, see Table 31. These data suggest a kyphotic posture is related to increased elastic load as measured by lung volume and decreased capacity of the respiratory pump as measured by respiratory muscle strength.

Table 30 Descriptive analysis of posture in people with Huntington's disease

	Pre-manifest HD **n=18**	**Manifest HD** **n=43**	**t-value** **p** **[95%CI]**
Thoracic angle° Mean ±sd [95%CI]	43.26 ±10.14 [38.21, 48.30]	51.95 ±13.30 [47.85,56.04]	t=-2.481 p=0.016 [-15.70,-1.68]
Neck angle° Mean ±sd [95%CI]	39.03 ±8.42 [34.84, 43.21]	26.16 ±52.78 [9.92, 42.40]	t=1.553 p=0.127 [-3.8, 29.55]
Head tilt° Mean ±sd [95%CI]	151.02 ±10.13 [145.98, 156.06]	123.10 ±68.18 [102.12, 144.09]	t=2.617 p=0.012 [6.45, 49.39]

Figure 31 Scatterplots of respiratory function against thoracic angle



FVC Forced vital capacity (litres)
MIP Maximal inspiratory pressure (cmH_2O)

Table 31 Relationships between respiratory function and thoracic angle

	R_s	R_s^2	p value
MIP% predicted	-0.551	0.304	<0.001
MIP	-0.526	0.277	<0.001
SNIP% predicted	-0.488	0.238	0.003
SNIP	-0.465	0.216	0.002
FVC% predicted	-0.465	0.216	0.002
FVC	-0.427	0.182	0.004
PCF	-0.388	0.151	0.016
FEV_1/FVC	0.032	0.001	0.837

MIP Maximal inspiratory pressure (cmH_2O)
SNIP Sniff nasal inspiratory pressure (cmH_2O)
FVC Forced vital capacity (litres)
PCF Peak cough flow (litres/minute)
FEV_1/FVC Forced expiratory volume in one second/forced vital capacity
R_s Spearman's correlation coefficient

5.5.3 Exercise capacity

Table 32 shows the distances walked during six minutes for people with pre-manifest HD and people with manifest HD, compared with data from Quinn et al 2013. The values for people with manifest HD is much lower in the current study compared to Quinn et al (2013) yet people with pre-manifest HD is similar. Predicted values for 6MWD were calculated from Enright and Sherrill (1998) 6MWD% predicted is significantly lower in people with manifest HD compared to people with pre-manifest HD ($t=10.55$, $p<0.001$ [41.25, 60.54]).

Table 32 Descriptive analysis of six minute walk distance

	Quinn et al (2013)	This study	6MWD% predicted for this study
Pre-manifest HD 6MWD mean ±sd [95% CI]	515.75 ±101.66 [447.5, 584.1]	503.39 ±88.51 [461.96, 544.81]	78.63 ±12.84 [72.62, 84.64]
Manifest HD 6MWD mean ±sd [95% CI]	381.66 ±129.97 [348.65, 414.67]	173.32 ±166.133 [123.99, 222.66]	27.73 ±26.29 [19.92, 35.54]

6MWD six minute walk distance (metres)

Data related to heart rate, respiratory rate, saturation of O_2, perceived dyspnoea and perceived exertion were taken before and after the six minute walk test, see Table 33. The data are incomplete for some variables.

Respiratory rate was slightly higher than the typical value of 12 at rest, but did not reach the typical rate of 30 for moderate exercise (McArdle et al. 2010), after the 6MWT. Observations whilst measuring respiratory rate noted that the rate was often irregular before the walking test, but became regular immediately afterwards. Heart rate before the test was typical for

untrained people (McArdle et al. 2010), with a small rise after the test. Desaturation did not occur during the walk.

Before the test, 70.8% of people with manifest HD had a perceived dyspnoea score of 0 (nothing at all) with 57.1% having a perceived exertion score of 6 (no exertion at all). The maximum pre-test score for perceived dyspnoea was 2 (slight), and exertion was perceived at a maximum of 15 (hard, heavy). After the walk, 87.0% of people perceived dyspnoea to be moderate (3) or less with 80% perceiving exertion to be somewhat hard (13) or less.

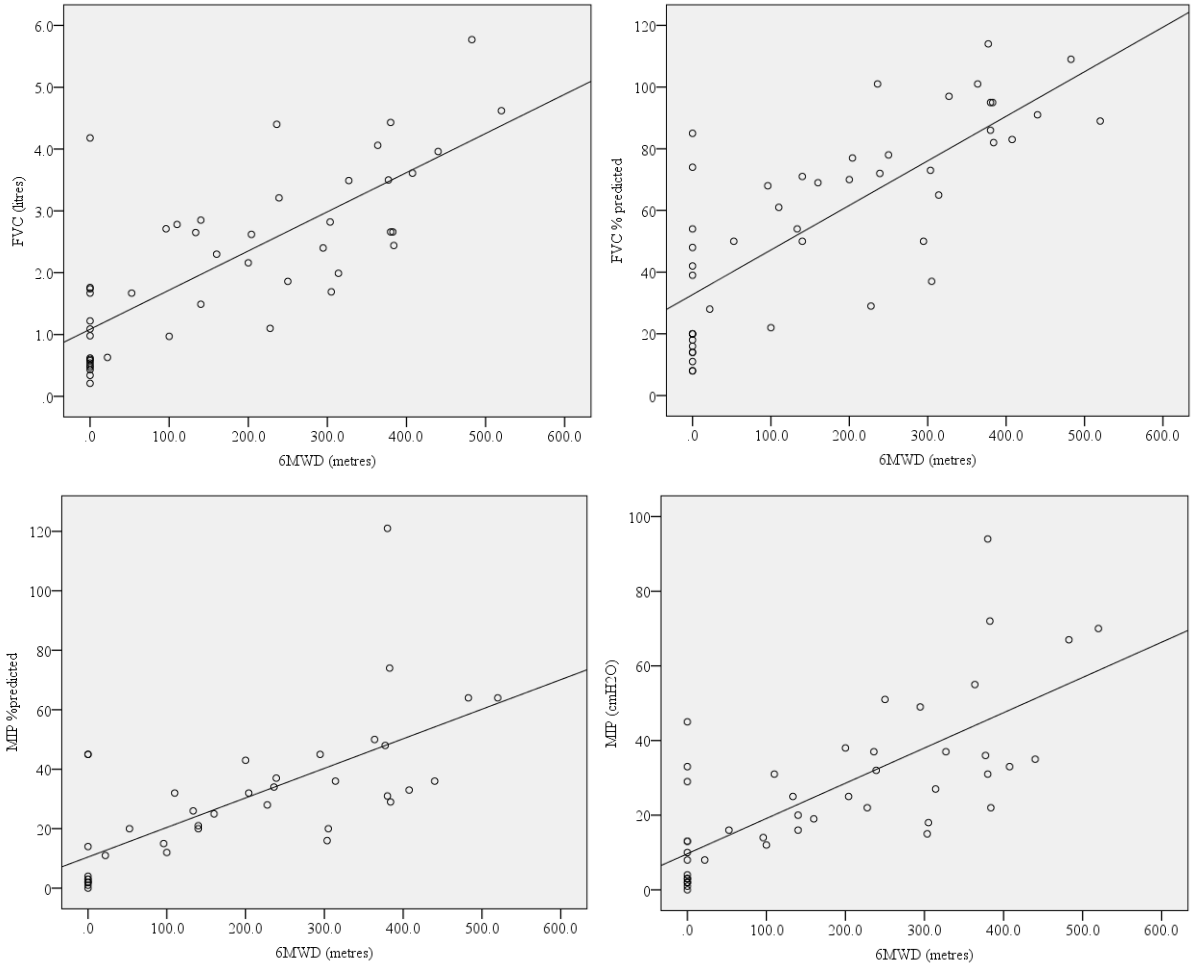
Table 33 Variables related to six minute walk test

	Before 6MWT	**After 6MWT**
Respiratory rate (breaths per minute)	15 ±5 n=29	19 ±6 n=18
Heart rate (beats per minute)	74 ±12 n=34	86 ±18 n=24
Saturation O_2 (%)	96 ±2 n=33	97 ±1 n=23
Perceived dyspnoea (0-10 scale)	Median 0 Range 0-2 n=24	Median 2 Range 0-7 n=23
Perceived exertion (6-20 scale)	Median 6 Range 6-15 n=21	Median 13 Range 6-17 n=20

6MWT six minute walk test

Scatterplots of respiratory function and distance walked in six minutes demonstrated positive relationships, see Figure 32. The relationships were significantly correlated: R_s ranged 0.504-0.780; R_s^2 ranged 0.254–0.608; $p<0.01$, see Table 34. This analysis was repeated for respiratory function % predicted values and % predicted six minute walk distance with similar results, see Table 35. These data indicate that decreased exercise tolerance is related to increased load i.e. low lung volume and decreased capacity of the respiratory muscles.

Figure 32 Scatterplots of respiratory function against 6 minute walk distance



FVC Forced vital capacity (litres)
MIP Maximal inspiratory pressure (cmH_2O)
6MWD six minute walk distance (metres)

Table 34 Relationships between respiratory function and 6 minute walk distance

	R_s	R_s^2	p value
FVC% predicted	0.780	0.908	<0.001
FVC	0.759	0.576	<0.001
MIP	0.746	0.557	<0.001
MIP% predicted	0.725	0.526	<0.001
SMIP	0.652	0.425	<0.001
SNIP	0.598	0.358	<0.001
SNIP% predicted	0.504	0.254	0.002

FVC Forced vital capacity (litres)
MIP Maximal inspiratory pressure (cmH_2O)
SMIP Sustained maximal inspiratory pressure (pressure time units)
SNIP Sniff nasal inspiratory pressure (cmH_2O)
Rs Spearman rank correlation coefficient

Table 35 Relationships between respiratory function and 6 minute walk distance % predicted

	R_s	R_s^2	p value
FVC% predicted	0.778	0.605	<0.001
MIP% predicted	0.711	0.506	<0.001
SNIP% predicted	0.245	0.060	0.001

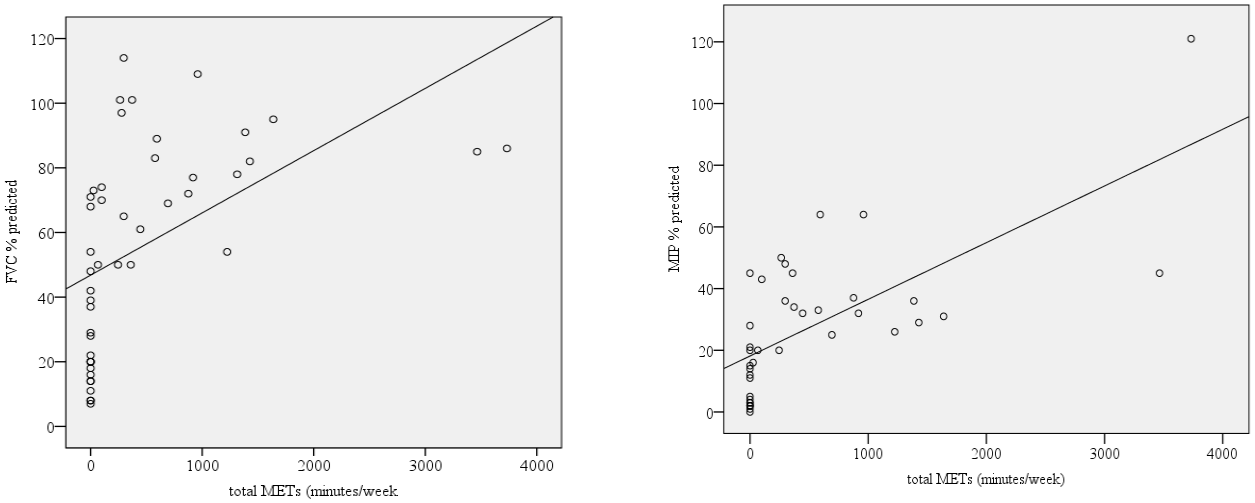
FVC Forced vital capacity (litres)
MIP Maximal inspiratory pressure (cmH_2O)
SNIP Sniff nasal inspiratory pressure (cmH_2O)
Rs Spearman rank correlation coefficient

5.5.4 Physical activity

Data collected from IPAQ allowed for categorical and continuous data to be analysed. Total METs min/week was categorised into high (>3000), moderate (601-2999) and low (<600). In people with HD, 10.61% (n=7) were categorised as high activity, 33.33% (n=22) as moderate and 56.10% (n=37) as low activity (IPAQ Research Committee. 2005). The median scores for people with pre-manifest HD and manifest HD were moderate, 1502.50 (IQR=2418.4), and low, 82.50 (IQR=618.80) respectively. Similar to exercise capacity, these results are lower than those found by Quinn et al. (2013) with mean values of 2649 ±2107 for people with pre-manifest HD and 1354 ±1796 for people with manifest HD.

Differences between people with pre-manifest HD and manifest HD were not analysed as IPAQ is recommended as a population surveillance measure rather than an outcome measure (IPAQ Research Committee. 2005). Scatterplots of respiratory function and total METs demonstrated positive relationships, see Figure 33. The relationships were significantly correlated: R_s ranged 0.627-0.790; R_s^2 ranged 0.276-0.624; $p<0.001$, see Table 36. These findings are similar to exercise capacity, with decreased physical activity being related to increased load and decreased capacity of the respiratory pump.

Figure 33 Scatterplots of respiratory function against total METs



FVC Forced vital capacity (litres)
MIP Maximal inspiratory pressure (cmH_2O)
METs Metabolic equivalents (minutes/week)

Table 36 Relationships between respiratory function and total METs

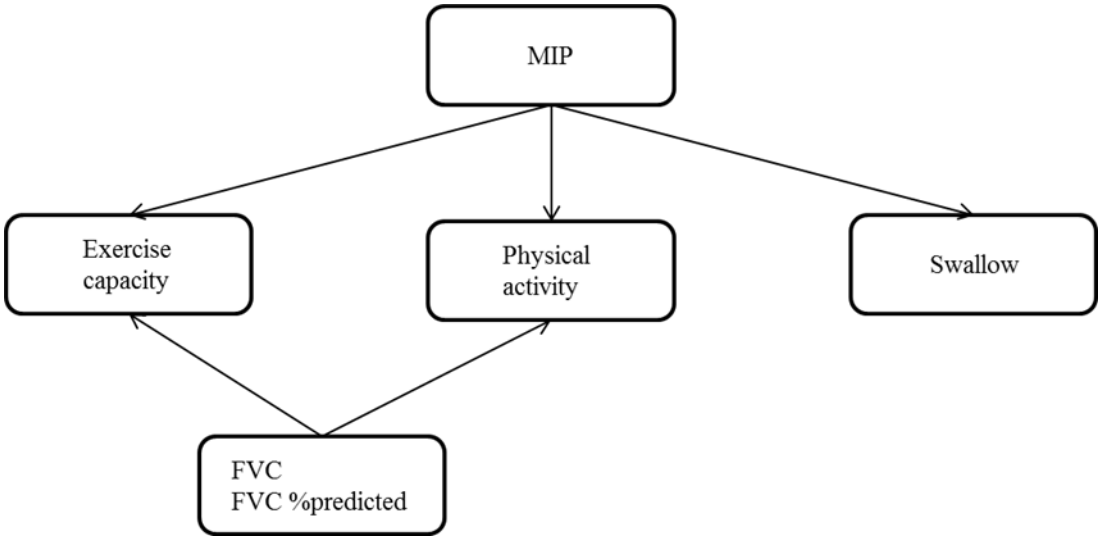
	R_s	R_s^2	p value
FVC% predicted	0.790	0.624	<0.001
MIP	0.775	0.600	<0.001
MEP	0.775	0.600	<0.001
SMIP	0.758	0.575	<0.001
FVC	0.755	0.570	<0.001
MEP% predicted	0.728	0.530	<0.001
MIP% predicted	0.725	0.526	<0.001
SNIP	0.627	0.393	<0.001
SNIP% predicted	0.525	0.276	0.001

FVC Forced vital capacity (litres)
MIP Maximal inspiratory pressure (cmH_2O)
MEP Maximal expiratory pressure (cmH_2O)
SMIP Sustained maximal inspiratory pressure (pressure time units)
SNIP Sniff nasal inspiratory pressure cmH_2O)
R_s Spearman's correlation coefficient

5.5.5 Summary of relational analysis

Respiratory function significantly correlated with swallow capacity, posture, exercise capacity and physical activity. The possibility of further exploration using linear regression was not carried out due to non-normal distribution of respiratory function data and the likelihood of colinearity. Using descriptors suggested by Portney and Watkins (2009), the data were reviewed for r values >0.75, indicating a good-excellent relationship. It was noted that forced vital capacity and inspiratory muscle strength demonstrated excellent relationships with exercise capacity and physical activity, with inspiratory muscle strength also demonstrating an excellent relationship with swallow capacity. This is illustrated in Figure 34. These results indicate that a complex relationship exists between respiratory function and exercise capacity, physical activity and swallow. The relationship between respiratory function and posture was fair to moderate.

Figure 34 Key relationships between respiratory function and influencing factors



MIP Maximal inspiratory pressure (cmH_2O)
FVC Forced vital capacity (litres)

5.6 Respiratory function and progression of Huntington's disease

The previous section investigated respiratory function in people with HD in the context of the framework of respiratory failure. Further analysis was undertaken to establish if respiratory function changed across the progression of the disease. This was achieved in two ways: the analysis of relationships between measures of disease severity and respiratory function and a follow up study with 10 people with manifest HD.

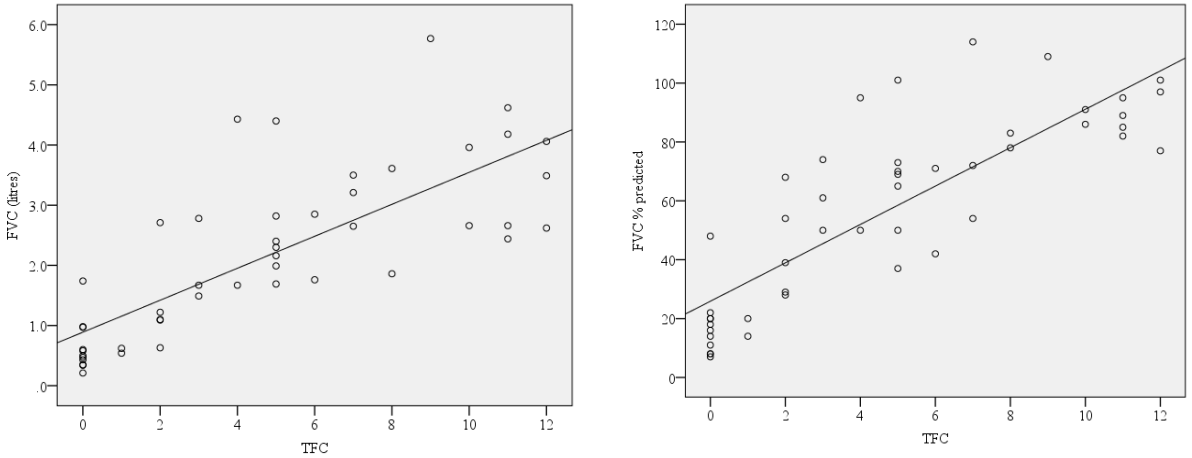
5.6.1 Relationship between disease severity and respiratory function

Disease severity was measured from functional (TFC) and motor (UHDRS:TMS) perspectives. Relationships were explored between these variables and all measures of respiratory function in people with manifest HD. Scatterplots of measures of respiratory function against TFC and against UHDRS:TMS demonstrated a positive relationship for all variables except FEV_1/FVC. This scatterplot showed no relationship between FEV_1/FVC and TFC. Typical scatterplots are shown in Figures 35-40.

All variables, except FEV_1/FVC, showed significant positive relationships with TFC and significant negative relationships with UHDRS:TMS. For TFC, R_s ranged from 0.716 (PCF)–0.863 (MIP); R_s^2 ranged from 0.513–0.745; $p<0.001$, see Table 37. For UHDRS:TMS R_s ranged from -0.625 (SNIP% predicted) to -0.874 (MIP% predicted); R_s^2 ranged 0.39 –0.824; $p<0.001$, see Table 38. These results indicate that respiratory function declines linearly as Huntington's disease progresses i.e. as TFC decreases and UHDRS:TMS increases.

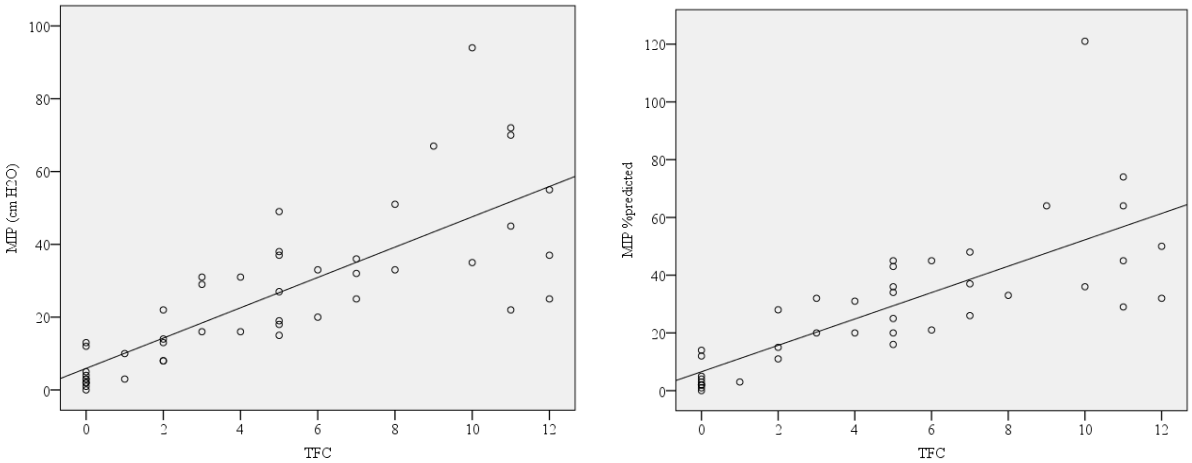
Further analysis was carried out to explore the relationship between PCF and TFC in order to predict when people with HD would have a PCF <270L/minute and therefore require interventional strategies to improve cough efficacy. Linear regression was used and a prediction equation generated: PCF=120.36 +27.91TFC. When PCF is 270, TFC is 5.36, i.e. middle stage of the disease suggesting that cough efficacy may be reduced when TFC <6.

Figure 35 Scatterplots of FVC and FVC% predicted against TFC



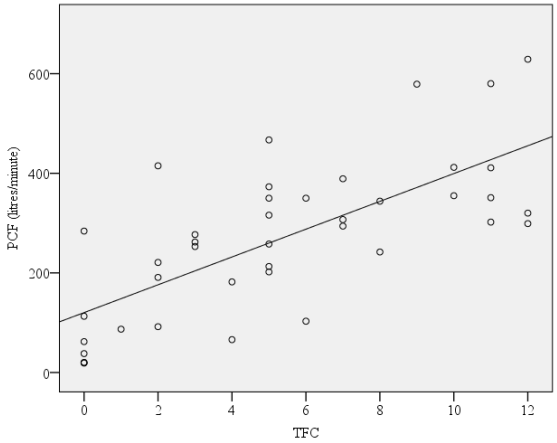
FVC Forced vital capacity (litres)
TFC Total functional capacity (0-12)

Figure 36 Scatterplots of MIP and MIP% predicted against TFC



MIP Maximal inspiratory pressure (cmH_2O)
TFC Total functional capacity (0-12)

Figure 37 Scatterplot of PCF against TFC



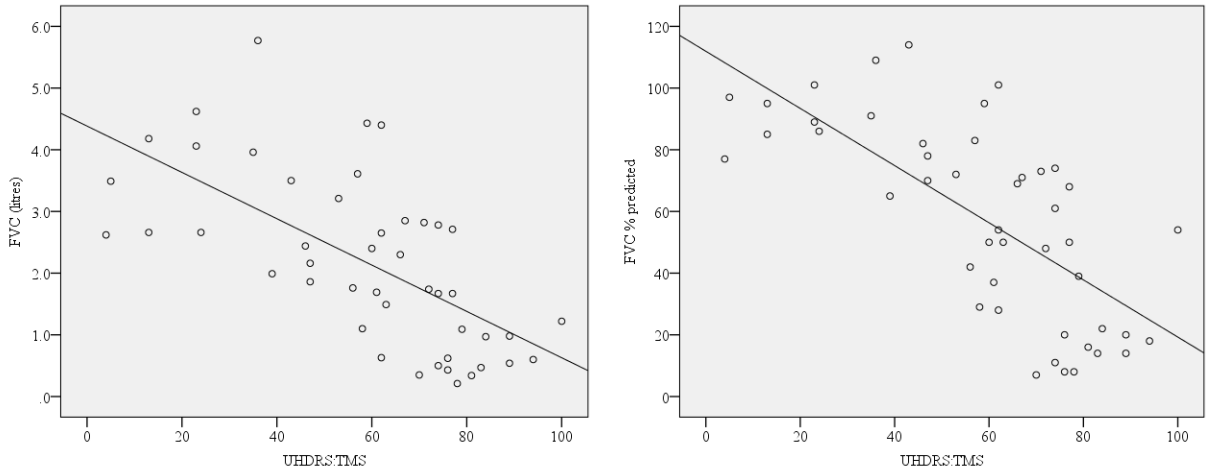
PCF Peak cough flow (litres/minute)
TFC Total functional capacity (0-12)

Table 37 Relationships between respiratory function and total functional capacity

	R_s	R_s^2	p value
MIP	0.863	0.745	<0.001
FVC% predicted	0.859	0.738	<0.001
MIP% predicted	0.854	0.729	<0.001
MEP	0.848	0.719	<0.001
MEP% predicted	0.832	0.692	<0.001
FEV_1% predicted	0.827	0.984	<0.001
FVC	0.819	0.671	<0.001
SNIP	0.806	0.650	<0.001
FEV_1	0.805	0.648	<0.001
SMIP	0.785	0.616	<0.001
SNIP% predicted	0.726	0.527	<0.001
PCF	0.716	0.513	<0.001
FEV_1/FVC	-0.231	0.053	0.119

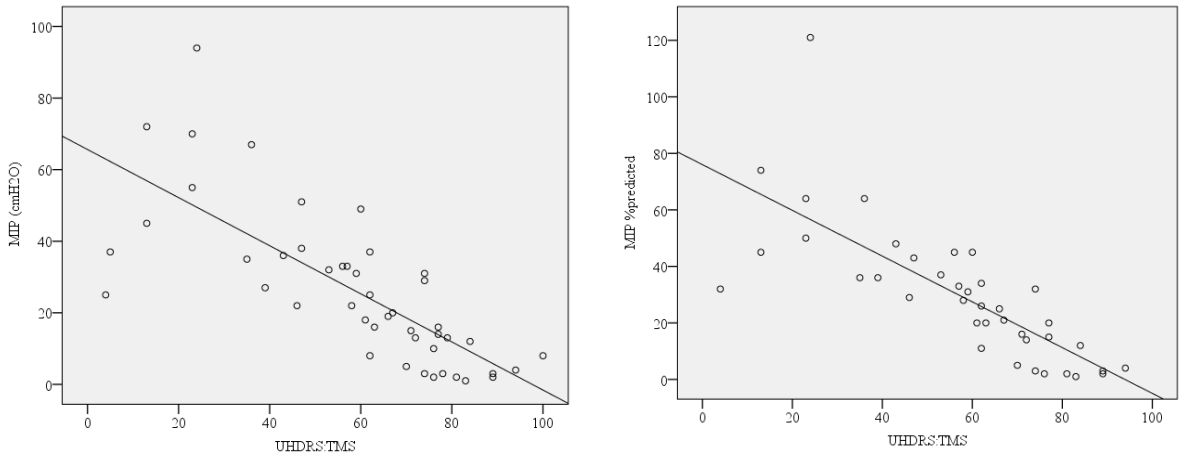
MIP Maximal inspiratory pressure (cmH_2O)
FVC Forced vital capacity (litres)
MEP Maximal expiratory pressure (cmH_2O)
FEV_1 Forced expiratory volume in one second (litres)
SNIP Sniff nasal inspiratory pressure (cmH_2O)
SMIP Sustained maximal inspiratory pressure (pressure time units)
PCF Peak cough flow (litres/minute)
R_s Spearman's correlation coefficient

Figure 38 Scatterplots of FVC and FVC% predicted against UHDRS: TMS



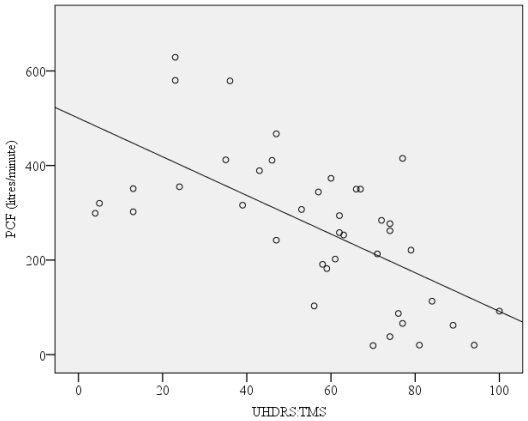
FVC Forced vital capacity (litres)
UHDRS:TMS Unified Huntington's disease rating scale: total motor score (0-124)

Figure 39 Scatterplots of MIP and MIP% predicted against UHDRS:TMS



MIP Maximal inspiratory pressure (cmH_2O)
UHDRS:TMS Unified Huntington's disease rating scale: total motor score (0-124)

Figure 40 Scatterplot of PCF against UHDRS:TMS



PCF Peak cough flow (litres/minute)
UHDRS:TMS Unified Huntington's disease rating scale: total motor score (0-124)

Table 38 Relationships between respiratory function and UHDRS:TMS

	R_s	R_s^2	p value
MIP% predicted	-0.874	0.764	<0.001
MIP	-0.842	0.709	<0.001
MEP	-0.814	0.663	<0.001
MEP% predicted	-0.812	0.659	<0.001
SMIP	-0.767	0.588	<0.001
FVC% predicted	-0.748	0.560	<0.001
FEV_1% predicted	-0.723	0.523	<0.001
FVC	-0.704	0.496	<0.001
FEV_1	-0.702	0.493	<0.001
SNIP	-0.693	0.480	<0.001
PCF	-0.670	0.449	<0.001
SNIP% predicted	-0.625	0.391	<0.001
FEV_1/FVC	-0.148	0.022	0.326

MIP Maximal inspiratory pressure (cmH_2O)
MEP Maximal expiratory pressure (cmH_2O)
SMIP Sustained maximal inspiratory pressure (pressure time units)
FVC Forced vital capacity (litres)
FEV_1 Forced expiratory volume in one second (litres)
SNIP Sniff nasal inspiratory pressure (cmH_2O)
PCF Peak cough flow (litres)
R_s Spearman's correlation coefficient

5.6.2 Respiratory function over time in people with Huntington's disease

Data were collected from 10 people with manifest HD approximately one year after the initial assessment, in order to determine if respiratory function decreased over a relatively short time period. The subjects, female=2, mean age 52.80 ±15.20, had a median TFC of 5 range 3-10 and mean UHDRS:TMS of 52.7 ±12.75. The average time gap between measurements was 15.5 months, range 12-19 months. Tables 39 and 40 provide analysis of respiratory function at initial assessment and at follow up. It is known that respiratory function declines with age, but normal rates of change are dependent on factors such as peak function in adulthood and the duration of plateau after 25 years of age. The estimated rate of decline of FEV_1 is 25-30ml per year from age 35-40 and may double after 70 years of age with a suggested 0.8–2.7cmH_2O decline in MIP per year in people aged 65-85 (Sharma and Goodwin 2006). The data from this study show a mean decline of 14ml in FEV_1 and 4cmH_2O decline in MIP, which would appear to be within a normal range. Statistically, there were no differences in respiratory function over one year in time.

Table 39 Lung volumes at initial assessment and follow up

	Initial assessment mean ±sd	Follow up mean ±sd	% change	Mean difference [95% CI] p value
FVC L	2.93 ±1.39	2.87 ±1.35	-2.05	-0.05 [-0.27,0.38] 0.725
FVC% predicted	70.40 ±24.23	69.10 ±25.93	-1.85	-1.30 [-7.44,10.04] 0.744
FEV_1 L	2.46 ±1.14	2.32 ±1.20	-5.69	-0.14 [-0.16,0.44] 0.316
FEV_1% predicted	73.30 ±24.59	70.40 ±28.93	-3.96	-2.90 [-6.90,12.70] 0.520
FEV_1/FVC	85.10 ±12.00	80.10 ±13.44	-5.88	-5.00 [-3.47,13.471] 0.215
PEFR L/min	279.00 ±132.40	268.90 ±147.04	-3.62	-10.9 [-52.68,74.48] 0.707
PEFR% predicted	54.90 ±20.37	54.60 ±25.21	-0.55	-0.30 [13.01,13.61] 0.960
PCF L/min	314.30 ±138.39	322.10 ±162.93	+2.48	+7.80 [-64.75,49.15] 0.764

FVC Forced vital capacity (litres)
FEV_1 Forced expiratory volume in 1 second (litres)
FEV_1/FVC Forced expiratory volume in 1 second/forced vital capacity
PEFR Peak expiratory flow rate (litres/minute)
PCF Peak cough flow (litres/minute)

Table 40 Respiratory muscle function at initial assessment and follow up

	Initial assessment mean ±sd	Follow up mean ±sd	% change	Mean difference [CI] p value
MIP cmH_2O	33.80 ±15.61	29.50 ±21.56	-12.72	-4.30 [-5.18,13.78] 0.332
MIP% predicted	37.50 ±14.07	30.13 ±22.61	-19.65	-7.38 [-4.86,19.61] 0.197
SNIP cmH_2O	34.33 ±15.40	35.33 ±12.73	+2.91	1.00 [-12.30,10.30] 0.843
SNIP% predicted	31.86 ±12.27	33.86 ±10.70	6.28	-2.00 [-16.09,12.09] 0.740
MEP cmH_2O	44.50 ±26.01	48.00 ±29.31	7.87	3.50 [-14.48,7.48] 0.489
MEP% predicted	32.37 ±22.73	34.13 ±20.73	5.44	1.75 [-12.28,8.78] 0.706
SMIP PTU	132.30 ±116.23	126.30 ±128.16	-4.53	-6.00 [-15.46,27.46] 0.543

MIP Maximal inspiratory pressure (cmH_2O)
SNIP Sniff nasal inspiratory pressure (cmH_2O)
MEP Maximal inspiratory pressure (cmH_2O)
SMIP Sustained maximal inspiratory pressure (pressure time units)

5.7 Summary of Observational Study

The observational study aimed to investigate: respiratory function in people with HD and compare this with healthy control subjects; respiratory function throughout the progression of HD and factors that may influence and be influenced by respiratory function in people with HD. The following null hypotheses were rejected:

H_{01} There is no difference in respiratory function in people with HD compared to healthy control subjects;

H_{02} Respiratory function in people with HD does not change as the disease progresses;

H_{04} Respiratory function is not related to exercise capacity in people with HD;

H_{05} Respiratory function is not related to physical activity in people with HD;

H_{06} Respiratory function is not related to posture in people with HD;

H_{07} Respiratory function is not related to swallow capacity in people with HD;

The following null hypothesis was not rejected:

H_{03} Respiratory function does not decrease over time;

The findings from this study indicate that respiratory function in people with manifest HD is decreased when compared to people who are pre-manifest and to healthy control participants and that respiratory function in people with manifest HD declines linearly with disease progression. Respiratory function is positively related to exercise capacity, physical activity, and swallow in people with manifest HD, with lower respiratory function also being associated with a more kyphotic posture. The following chapter will discuss these findings in the context of the proposed framework of respiratory failure in people with HD.

6 Observation Study discussion

6.1 Overview of observation study findings

This study has identified that respiratory function in people with manifest Huntington's disease is decreased when compared to a matched healthy control group. Furthermore it is apparent that this decreased function is linearly associated with disease severity. Exploration of relationships between respiratory function and potential influencing factors identified excellent relationships between respiratory function and exercise capacity; physical activity and swallow capacity. In the context of the proposed framework of respiratory failure in HD, the results of this study suggest that people with HD are susceptible to type 1 hypoxaemic respiratory failure and predisposed to type 2 hypercapnic respiratory failure. Type 1 hypoxaemic respiratory failure due to aspiration pneumonia is likely to be due to impaired swallow capacity and ineffective cough. Decreased lung volume leading to hypoventilation will influence type 1 hypoxaemic respiratory failure with progressive decline leading to the development of type 2 hypercapnic respiratory failure. Predisposition to type 2 respiratory failure is due to decreased capacity of the respiratory muscle pump and increased elastic and resistive load due to decreased lung volume and upper airway dysfunction respectively. Decreased respiratory muscle strength may be directly attributable to HD pathology and/or be influenced by other factors. Inspiratory muscle strength demonstrated excellent relationships with exercise capacity, physical activity and swallow capacity; expiratory muscle strength demonstrated an excellent relationship with physical activity as did respiratory muscle endurance. The relationship between inspiratory muscle strength and posture was moderate to good. Decreased lung volume leading to increased elastic load may be as a consequence of decreased respiratory muscle strength with lung volume demonstrating excellent relationships with exercise capacity and physical activity, with a moderate to good relationship with swallow and only a fair relationship with posture. Increased resistive load was identified as upper airway obstruction in 50.7% of all participants and suggested by visual analysis of flow volume loops.

6.2 Discussion of observation study findings

The sample of people with manifest HD recruited to this study was skewed toward people who were more affected by HD, despite considerable effort by the researcher. The researcher attended the weekly HD research and management clinic for three years and discussed recruitment issues with the clinician responsible for the patient group and the research nurse. The researcher also attended the HD Association study days and AGM to discuss and disseminate information regarding the research. A number of reasons may explain the lack of people with early stage HD attending clinic appointments. It is possible that people beginning to show signs and symptoms may be in denial and do not wish to undergo assessment that may confirm clinical diagnosis of the condition. This may be due to an individual's way of dealing with a genetic neurodegenerative condition as well as the continuing stigma associated with the condition. Wexler (2010) feels that the shame and embarrassment felt by family members at public hearings in the United States in 1977 still pervade the HD community today. For people newly diagnosed with HD without a family history, confirmation may be extended and the person may be at the middle stage of disease, before attending a HD specific clinic.

People with HD were categorised as people with pre-manifest and manifest HD based on neurological assessment by a neurologist. This was based upon the UHDRS:TMS and a diagnostic confidence level of 4 (motor abnormalities that are unequivocal signs of HD ≥99% confidence). There was some overlap in scores between the people with pre-manifest and manifest HD, 0–15 and 4–100 respectively, which indicated that although motor impairment was noted in some people with pre-manifest HD, they were not showing signs unequivocal of HD. This overlap was also noted in the PHAROS study, when the same categorisation criteria were used (Marder et al. 2009). All people with pre-manifest HD were functionally able and independent as observed by TFC, functional assessment, independence scale and Barthel Index. The full range of severity of HD was observed in the people with manifest HD as measured by disease specific scores, see Table 4. Twelve people lived in a nursing home, the remainder at home with or without some level of support.

Recruitment of healthy control participants was on-going alongside that of people with HD with carers and relatives being approached - 12 consented to participate in the study. Other healthy control participants were recruited from staff and students from within Cardiff University and also from friends and relatives of staff at the university, in order to achieve matching of the groups for confounders of respiratory function. Healthy control recruitment

raises a number of issues. Ideally these participants should be matched to the comparator group i.e. those with HD, in order to eliminate the influence of extraneous variables. University students are not representative of the lifestyle of the general population and in particular the students in this study were predominantly physiotherapy students. Carers and relatives of participants may lead a more similar lifestyle to people with HD, but there is also the issue that their lifestyle may be indirectly affected by caring for someone with a health condition. The healthy control group in this study therefore contained a mixture of carers, relatives and university staff and students and matched people with HD for confounding variables of respiratory function i.e. age, gender, smoking habit and fat free mass, see Table 3.

The findings of this study are now discussed in relation to the proposed framework of respiratory failure in people with HD. The framework was based on the categorisation described by Hart (2008) and developed through theoretical postulation regarding HD pathology and evidence from people with PD, MS and MND/ASLMS. The primary cause of respiratory failure in people with neurodegenerative conditions is thought to be decreased capacity leading to type 2 hypercapnic respiratory failure (Buyse 2006), but impaired swallow and ineffective cough may also predispose to aspiration pneumonia and type 1 hypoxaemic respiratory failure. These factors are then related to the functional problems of decreased ventilatory capacity, decreased respiratory muscle strength and decreased cough efficacy leading to retained secretions.

6.2.1 Type 1 hypoxaemic respiratory failure

The participants in this study were all medically well and did not show any signs of type 1 hypoxaemic respiratory failure as demonstrated by heart rate, respiratory rate and O_2 saturation values being within normal range, see Table 6. A small proportion of the participants had presented with symptoms of respiratory problems in the preceding year, 2 (10%) people with pre-manifest HD and 11 (23.4%) people with manifest. The number of GP visits is slightly higher than that for the general population in Wales at 14% (Welsh Government 2012), reflecting the increased incidence of clinical respiratory problems in the later stages, as the TFC for those with chest infections was 0-5. Uptake of flu vaccination was 47.7% which is surprisingly low in an at risk sample with average age of 53 years, although this was similar to figures for Wales in people less than 65 with one or more clinical risk factor (49.7%) (Public Health Wales 2014). Dyspnoea, as a key symptom in respiratory disease, was not evident at rest when measured by the modified Borg dyspnoea scale.

The findings of abnormal swallow, decreased cough efficacy and decreased lung volume support the proposition in the conceptual framework that people with HD are susceptible to type 1 respiratory failure.

This is the first study to quantify swallow capacity in people with HD and the decreased swallow capacity values concur with short oral transit time described by Heemskerk and Roos (2011). Objective measures of swallow capacity indicated that only 7 (15.2%) people with manifest HD had normal swallow capacity, the mean % predicted values being 28 ±34.35 based on Hughes and Wiles (1996). Swallow dysfunction is recognised in people with HD (Kagel and Leopold 1992) but the underlying mechanisms are unknown. Although the exact integrative swallow and breathing mechanisms are unknown, the anatomical closeness in the brainstem of the two control centres, and proximity to the nucleus of the hypoglossal nerve innervating the tongue could infer functional integration. The % predicted values for volume per swallow were higher than those for swallow capacity (47.07 ±41.46), which highlights that for some people (n=15) timing of swallow was an issue and others (n=17) had either a volume or volume and timing issue. This may indicate that central generation of swallow may be affected in people with HD with impairment of appropriate integration between breathing and swallowing. Automatic respiratory rhythm is generated in the pontomedullary region of the brainstem (Hudson et al. 2011) with projections to the inspiratory muscles, expiratory muscles and activation of the laryngeal and tongue muscles which act as valves modulating airflow (Feldman et al. 2013). The anatomical proximity of hypoglossal nerve and the respiratory nuclei and the identification of brainstem pathological changes (Herndon et al. 2009; Hobbs et al. 2010; Rub et al. 2014) in people with HD would support this finding. Evidence that P_aO_2 influences swallow and breathing and pharyngeal dysfunction influences breathing (Hårdemark Cedborg et al. 2009) adds strength to this proposition. Evidence of abnormalities in tongue protrusion (Reilmann et al. 2010), swallow dysfunction (Heemskerk and Roos 2011) and the presence of mutant Huntingtin in the brainstem (Herndon et al. 2009) may provide some insight into control of breathing in people with HD and help to explain the relationship, see Table 28 between swallow and respiratory function observed in this study.

Normal swallow is both a reflex and planned manoeuvre involving not only the swallow mechanism but also pulmonary function and situational factors. Appropriate integration between breathing and swallow and situational factors such as food preparation, appropriate posture as well as adequate protective mechanisms are necessary for safe and effective oral feeding (Hughes 2012; Hughes and Wiles 2000). Data from the swallow questionnaire see

Table 7 indicates that people with manifest HD modify situational factors i.e. specially preparing their food (65%), adapt behaviourally by avoiding certain foods (60%) and compensate by drinking water whilst eating (50%) to ensure safe passage of food. People with manifest HD in this study were aware that food did go down the wrong way and that they coughed when eating and therefore these modifications were made to minimise the risk of aspiration. Although people may be aware of potential large aspirations, they may be unaware of micro aspiration. Normal swallow capacity was identified in only 7% of people with manifest HD, yet 32.5% reported no problems with coughing during eating or food going down the wrong way.

This study has established that swallow capacity is reduced in people with manifest HD and that this is adjusted for by modifying situational factors such as food preparation and eating behaviour. Furthermore, significant relationships were found between swallow capacity and respiratory function, and in particular inspiratory muscle strength. This may be due to each variable declining independently with disease progression but may reflect dysfunction in the integration of swallow and breathing.

From a clinical perspective, swallow dysfunction, decreased respiratory muscle strength and decreased peak cough flow increases the likelihood of type 1 hypoxaemic respiratory failure in people with HD. The consequence of aspiration pneumonia may be alleviated if cough mechanisms are effective in clearing secretions from the respiratory system. PCF in people with manifest HD in this study was significantly decreased compared to people with pre-manifest HD and healthy control participants, see Table 9 and correlated significantly with swallow capacity ($r=0.515$, $p<0.001$). From a clinical perspective, the most important finding is that the mean PCF in people with manifest HD was at the cut-off point necessitating interventions to enhance cough efficacy (Bott et al. 2009). The combination of impaired swallow and cough efficacy in people with manifest HD-increases the likelihood of aspiration pneumonia. This may lead to type 1 hypoxaemic respiratory failure due to impaired diffusion as a consequence of retained secretions and/or atelectasis leading to alveolar hypoventilation. Atelectasis may be the underlying cause of decreased volume found in people with manifest HD (56.70%predicted FVC), see Table 17. Concomitant decreased lung volume and silent aspiration may be underlying factors of a downward spiral of respiratory dysfunction. As lung volume decreases, closing volume will exceed end expiratory volume resulting in further airway closure (Milic-Emili et al. 2007), with repeated closure and re-opening of airways causing sheer stress within the airway and cell injury (Bian et al. 2010). Cell damage due to these biomechanical factors and inflammation as a consequence of aspiration (Wallis

and Ryan 2012) will lead to further hypoventilation and eventual hypoxaemia. This is compounded by the high incidence of smoking in people with HD (Byers et al 2012) which facilitates adherence of bacteria to lower airway epithelium and impairs mucociliary clearance. The decreased lung volume seen in people with manifest HD will result in hypoventilation, ventilation perfusion mismatch and decreased gaseous exchange that may contribute to type 1 hypoxaemic respiratory failure. Compared to an aspiration event which may result in acute hypoventilation and hypoxaemia, decreased lung volume due to progressive atelectasis could represent an underlying respiratory dysfunction that may contribute to an acute episode of hypoxaemia, and by progressively increasing elastic load contribute to the development of type 2 hypercpanic respiratory failure.

The findings of this study corroborate evidence that swallow dysfunction exists in people with manifest HD which may lead to aspiration of food or liquid. The data from this study indicate that people with HD are susceptible to type 1 hypoxaemic respiratory failure which is caused either by escalating hypoventilation and micro aspirations and/or a single large aspiration due to swallow dysfunction and retention of secretions due to ineffective cough. The decline in lung volume and cough efficacy concomitant with disease progression indicates the need for monitoring of respiratory function. The outcome of linear regression of PCF with TFC highlights that cough becomes ineffective when TFC is less than 5, therefore clinical observation of swallow and cough should be carried out during the middle stage of the disease.

6.2.2 Type 2 hypercapnic respiratory failure

Type 2 hypercapnic respiratory failure results from an imbalance between neural respiratory drive, the load on the respiratory system and respiratory muscle capacity (Hart 2008). For people with neurodegenerative conditions, respiratory muscle weakness leading to decreased capacity is suggested as the main problem, although increased load due to reduced chest wall and pulmonary compliance, upper airway weakness and impaired control of breathing may also alter the balance between drive, capacity and load (Buyse 2006; Misuri et al. 2000). Clinical characteristics of type 2 hypercapnic respiratory failure are difficulty sleeping, sleepiness during the day and morning headaches (Polkey et al. 1999). Blood gas analysis was not carried out in this study and although there was evidence of difficulty in sleeping (people with pre-manifest HD 45.0%, manifest HD 28.9%) and daytime sleepiness (people with pre-manifest HD 70.0%, manifest HD 57.5%), morning headache was not common (people with pre-manifest HD 20.0%, manifest HD 15.5%). The low frequency of morning

headache would suggest that these findings are more likely due to altered sleep patterns in people with HD rather than nocturnal hypoventilation. These findings add to previous studies on sleep related breathing disorders which are not conclusive regarding abnormal breathing pattern (Arnulf et al. 2008; Cuturic et al. 2009; Wiegand et al. 1991), with only a small study with no control group showing abnormalities in people with late stage disease (Antczak et al. 2013). It is still unclear as to whether sleep and circadian rhythm disruption in people with HD are due to direct gene involvement or as a consequence of having a neurodegenerative condition (Morton 2013). Nocturnal monitoring of sleep and arterial blood saturation patterns may help to identify whether the problems relate to underlying HD pathology or decreased ventilatory capacity. Although there were few clinical signs or symptoms of type 2 hypercapnic respiratory failure in this sample, this study provides the first evidence that capacity is decreased and load increased in people with manifest HD that may predispose to type 2 hypercapnic respiratory failure.

Subjective data collected via questionnaire suggest that people with manifest HD had more difficulties in coughing and clearing secretions than people with pre-manifest HD, see Table 7, reflecting the objective data regarding PCF. The ability to cough requires both adequate inspiratory muscle strength to increase lung volume and adequate expiratory muscle strength to produce sufficient flow to clear secretions (McCool 2006), therefore decreased PCF may occur as a consequence of weakness in both groups of muscles.

Breathlessness, as a symptom of inspiratory muscle weakness, was evident in 38.3% of people with manifest HD and 50.0% of people with pre-manifest HD. In people with pre-manifest HD, this symptom was felt only sometimes and tended to occur on exertion, i.e. walking uphill, walking or running. Breathlessness at rest was felt by three people with manifest HD but was not a constant symptom. This is supported by a median score of no breathlessness in the modified Borg dyspnoea scale when measured at rest for both people with pre-manifest and manifest HD. The data suggest that breathlessness was not a predominant clinical problem in this sample, yet this is in conflict with objective data of decreased inspiratory muscle strength, as MIP was found to be 29.31%predicted (mean value) in people with manifest HD. This could be due to an impaired respiratory drive response to hypercapnia or low activity masking respiratory insufficiencies as found in people with PD (Haas et al. 2004; Seccombe et al. 2011; von Klaveren et al. 1999). The integration of information relating to breathlessness i.e. physiological and psychological (Parshall et al. 2012) may be impaired in people with HD similar to that found in neuromuscular patients with primary muscle disorders (Hours et al. 2004), which may be due to either altered chest

wall motion or altered response to hypercapnia (Seccombe et al. 2011; von Klaveren et al. 1999). Altered input to the pons from pulmonary mechanoreceptors and to the medulla from chemoreceptors and peripheral mechano receptors may influence the integration of information related to respiratory effort and may therefore effect the sensation of dyspnoea.

Objective measures of respiratory muscle strength demonstrated significantly decreased inspiratory and expiratory muscle strength in people with manifest HD compared to people with pre-manifest HD and healthy control participants, see Table 12 concurring with evidence from Reyes et. al (2014). The extent of inspiratory and expiratory muscle weakness was similar with mean values of MIP 29.31%predicted, SNIP 36.65%predicted and MEP 29.06%predicted. MIP and SNIP measures do not discriminate between the strength of the diaphragm and that of other inspiratory muscles (American Thoracic Society/European Respiratory Society. 2002). Specific weakness of the diaphragm can be identified by measuring FVC in supine and sitting position, with normal subjects reducing FVC by 5-10% in the supine position, a decrease of >30% indicating severe diaphragm weakness (American Thoracic Society/European Respiratory Society. 2002). The results indicated that five individuals had a FVC supine <70% FVC sitting. Three participants were late stage (TFC = 0) with very low FVC% predicted, 8-22 therefore these results may be due to general weakness. It is difficult to explain the findings for the two participants in the middle stage, both of whom were independently mobile, with one getting short of breath only when walking hills. These findings may be simple anomalies. It would appear that, in this study, decreased MIP and SNIP was due to global respiratory muscle weakness rather than specific diaphragm weakness.

Respiratory muscle strength in people with HD may be influenced by HD pathology within the central nervous system and skeletal muscle but also by exercise capacity, physical activity and posture as identified in this study.

Cortico-striatal dysfunction leading to chorea, dystonia and bradykinesia may impact on the quality of respiratory muscle contraction. Motor control of voluntary movement via the cortico-spinal pathway in people with HD is affected by the loss of medium spiny neurons, resulting in chorea in the early stages of the condition followed by bradykinesia and rigidity (Andre et al. 2010; Han et al. 2010). Chorea and bradykinesia may influence the biomechanical effectiveness of the respiratory muscles, through altered force production and altered co-ordination of contraction. The integrated role of the abdominal and respiratory muscles in postural and ventilatory roles may also influence force production. Respiratory

dysfunction has been seen to alter posture in people with COPD (Janssens et al. 2013) and low back pain influences diaphragm contraction (Kolar et al. 2012) and therefore links between postural instability in people with HD (Brozova et al.2011) and respiratory muscle strength could be suggested. This evidence of poor postural control may be in part due to diaphragm dysfunction or conversely diaphragm dysfunction may be due to postural instability. More specifically, the ability of the diaphragm to fix against abdominal contents may be influenced by the stability of the trunk, with truncal chorea and dystonia potentially affecting the biomechanical efficiency of diaphragm contraction.

Physiological factors influencing force generation in muscles in people with HD include emerging evidence of altered membrane potential and hyperexcitability (Waters et al. 2013), muscle atrophy and secondary effects of malnutrition. Mutant Huntingtin has been found in animal (Orth et al. 2003) and human (Sassone et al. 2009) muscle studies, yet the relationship between mutant Huntingtin and muscle dysfunction is unclear. It is suggested that mutant Huntingtin is a factor that results in mitochondrial dysfunction (Ciammola et al. 2011) causing an energy deficit that, in combination with increased protein synthesis, is part of a complex interaction leading to muscle atrophy (She et al. 2011). This evidence is based on animal and human studies on peripheral skeletal muscle, but if the premise of peripheral muscle strength as a surrogate for respiratory muscle strength (Buchman et al. 2008) is true, then the skeletal muscle atrophy observed in people with HD (Sassone et al. 2009) could be extended to include the respiratory muscles. Weight loss and cachexia noted in late stages of HD (Aziz and Roos 2013) may contribute to respiratory muscle atrophy as in other malnutritioned states as diaphragm weight loss is proportional to skeletal muscle weight loss (Polla et al. 2004). Atrophy of the diaphragm, as measured by diaphragm thickness, has a positive relationship with respiratory muscle strength in healthy subjects (DePalo et al. 2004) and people with respiratory conditions (Enright et al. 2007; Vestbo et al. 2006). If these physiological factors lead to the findings of reduced peripheral muscle strength (Busse et al. 2008), then the same physiological changes may lead to reduced respiratory muscle strength in people with HD.

Concomitant with decreased inspiratory and expiratory muscle weakness was a significant decrease in single breath work capacity in people with manifest HD with SMIP values 23.26% of healthy control; the values were also greatly reduced compared to those in healthy control participants in other studies (Enright et al. 2006b; Ionescu et al. 1998). The measure of single breath work capacity provides information relating to inspiratory muscle work throughout the full range of muscle length i.e. from residual volume to total lung capacity and

may reflect reduced respiratory muscle endurance (Enright et al. 2006a). SMIP (23.26%) was reduced more than MIP (36.39%) compared to the healthy control subjects which may indicate a loss of slow twitch compared to fast twitch fibres. This differs from evidence in animal and human studies of HD skeletal muscle (Strand et al. 2005) and findings in people with COPD (Levine et al. 2013) were the proportion of slow twitch fibres increased while the proportion of fast fibres decreased. These findings may reflect the different mechanisms within respiratory muscles and pathology of different conditions as decreased use of respiratory muscles in people who were mechanically ventilated demonstrated a decrease in all fibre types (Mantilla and Sieck 2013).

Respiratory muscle strength demonstrated an excellent positive relationship with exercise capacity (R_s 0.746) and physical activity (R_s 0.775) with a weaker relationship found with thoracic angle (R_s -0.526) indicating that secondary factors other than central nervous system and skeletal muscle pathology may impact on respiratory function. These factors are discussed in more detail in section 6.2.3.

The findings of decreased respiratory muscle strength from this study are similar to those from studies in people with PD, MS and ALS Observational studies in people with MS and PD show MIP values ranging from 27-77%, predicted (Buyse et al.1997; Gosselink et al. 2000; Mutluay et al. 2005) and MEP values in people with ALS (Polkey et al. 1998; Sathyaprabha et al. 2009); MS, 30-50%predicted (Buyse et al. 1997; Gosselink et al. 2000; Smeltzer et al. 1992) and PD, 38%predicted (Sabate et al. 1996). This co-existence of inspiratory and expiratory muscle weakness observed in people with HD, PD and MS suggests a global weakness of respiratory muscle. Decreased respiratory muscle strength and single breath work capacity in people with manifest HD signifies decreased capacity of the respiratory muscle pump. Inspiratory insufficiency will impact on ventilatory capacity which may influence both type 1 hypoxaemic respiratory failure and type 2 hypercapnic respiratory failure, with expiratory insufficient influencing the ability to clear secretions through an effective cough.

Sufficient expiratory muscle strength is needed for an effective cough and a correlation has been identified between PCF and MEP in people with neuromuscular and neurodegenerative conditions (Chatwin et al. 2003; Sancho et al. 2007; Trebbia et al. 2005) although in people with ALS, this is only apparent when there is substantial muscle weakness (Polkey et al. 1998). Abdominal muscles used in forced expiration may be weak due to incoordination or postural instability, a key motor issue in people with HD (Brožová et al. 2011). These

findings may explain the significant reduction in PCF in people with manifest HD compared to people with pre-manifest HD and healthy control participants.

Concomitant with observations of decreased capacity, the data from this study provide evidence that both elastic and resistive load are increased in people with HD, which predisposes people with HD to type 2 hypercapnic respiratory failure. Approximately two-thirds of the work of breathing in healthy subjects is due to overcoming elastic load that is related to lung tissue and chest wall compliance (Bach and Kang 2000). Decreased lung volume results in decreased alveolar compliance (Dargaville et al. 2010) leading to an increase in elastic load and consequent increase in the work of breathing. Although lung tissue compliance was not measured directly in this study, measures of lung volume were used as an indicator of compliance and thus load. Measures of forced vital capacity (FVC) were greatly reduced in people with manifest HD; mean % predicted 56.70 ±31.69. The large standard deviation in the current study may be accounted for by the wide range of disease severity in the sample. These findings are similar to studies on people with ALS, (FVC%predicted 49.6% ±18.9, Sathyaprabha et al 2009) and in a study on people with MS who were non-ambulatory (FVC%predicted 43%±26, Gosselink et al 2000). The findings are not consistent across all neurodegenerative conditions. Conflicting evidence in people with PD demonstrated decreased FVC compared to healthy controls (Sathyaprapbha et al 2005); significantly lower than predicted values (Sabate et al 1996) and no difference between actual and predicted values (Canning et al. 1997). Evidence in people with mild to moderate MS demonstrated normal FVC but did identify some individuals with %predicted values <80% (Altintas et al. 2007; Foglio et al. 1994; Koseoglu et al. 2006; Mutluay et al. 2005). From a pathological perspective, ALS has both central and peripheral nervous system involvement (Cooper-Knock et al. 2012) and therefore respiratory muscle dysfunction is theoretically more likely due to transmission deficiency compared to conditions such as PD.
The decrease in ventilatory capacity as noted by FVC values seen in people with manifest HD may be the consequence of a number of underlying mechanisms. Decreased physical activity (Busse et al. 2009; Quinn et al. 2013) may lead to a sedentary lifestyle with potential decrease in periodic deep breaths leading to micro atelectasis (Bach and King 2000). Reduction in stretch of the alveoli will lead to a reduction of surfactant production, subsequent decreased compliance and further alveoli collapse (Amin et al. 2013). The escalation of atelectasis will lead to decreased lung volumes and increased elastic load. Concomitant with this decreased respiratory muscle strength may contribute to a restrictive

respiratory pattern seen in people with neuromuscular conditions (Simonds 2013). A restrictive pattern is characterised by a concomitant decrease in FVC and FEV_1, which was observed in people with manifest HD in this study: FVC%predicted 56.70; FEV_1%predicted 60.51 with a trend toward an increasing FEV_1/FVC in people with manifest HD compared to people with pre-manifest HD and healthy control participants. The reduction in lung volumes in people with respiratory muscle weakness is thought to be due to a decrease in distending pressure generated by the respiratory muscles, but also to the secondary changes in chest wall compliance as a consequence of respiratory muscle weakness (De Troyer et al. 1980). Progressive decreasing lung volume and consequent hypoventilation may lead to chronic hypoxaemia. In people with chronic respiratory disease this leads to widespread hypoxic pulmonary vasoconstriction with potential right sided heart failure (Evans et al. 2011). This may have implications within HD when the causes of cardiac failure are as yet unknown (Abildtrup and Shattock 2013). Thus a downward spiral of respiratory muscle weakness leading to decreased lung volume and consequential altered biomechanics compounds respiratory function.

The decreased FEV_1 observed in people with manifest HD was accompanied by a relatively larger decrease in PEFR see Table 22, suggestive of large rather than small airway obstruction. This was further confirmed with analysis of FEV_1/PEFR showing that 55.3% of people with manifest HD and 40% of people with pre-manifest HD had upper airway obstruction and thus suggests increased resistive load in people with HD. Analysis of the flow volume loops indicates that the obstruction in people with pre-manifest HD tended to be laryngeal/pharyngeal in nature (39% n=7) whereas in people with manifest, vocal cord dysfunction was the most common cause of obstruction (42% n=18). These findings can be related to abnormal swallow identified within this study and evidence that swallow and speech is affected in people with HD. Laryngeal and pharyngeal dysfunction has been identified in swallow studies (Heemskerk and Roos 2011) accompanied by vocal cord dysfunction in a speech study (Rusz et al. 2013). The severity of laryngeal dysfunction is related to severity of motor impairment and due to underlying pathological changes in the striatum. Hyper-adduction of the vocal cords may be due to motor impersistence, similar to inability to maintain tongue protrusion (Rusz et al. 2013).

Reduced FEV_1 has been observed in people with PD and ALS, but is likely to be due to a restrictive rather than obstructive mechanism as FVC was also reduced (Sathyaprabha et al. 2005; Sathyaprabha et al. 2009), with normal values being observed in people with MS (Altintas et al. 2007; Foglio et al. 1994; Koseoglu et al 2006). Similar to this study, reduced

FEV_1 was accompanied by reduced PEFR in people with PD and ALS (Sathyaprabha et al. 2005; Sathyaprabha et al. 2009), which may indicate upper airway resistance to airflow. Although truncation of the flow volume loop suggests vocal cord involvement (Watson et al. 2009), the characteristic 'saw tooth' irregular flow seen in people with PD was not observed in this study. This oscillatory flow volume pattern see Figure 6, is thought to be due to vocal cord tremor or instability of the upper airway (Buyse 2006; Vincken et al. 1986). The irregular flows seen in this study have lower frequency oscillations which could be due to either choreic movement of the diaphragm if seen on inspiration or of the abdominal muscles during expiration. Choreic movements of the diaphragm occurring during voluntary breathing, such as these respiratory assessment tasks, may be due to lack of integration in the striatum of the cortico-spinal pathways. Whether these movements occur during involuntary or adaptive breathing would be difficult to assess. Abnormalities on expiration may be associated with a lack of synchrony between respiratory and abdominal muscles, with respiratory muscles having a postural role (Bianchi and Gestreau 2009) and abdominal muscle providing stability of the abdominal contents during inspiration (Gauthier et al. 1994) as well as having a role in active expiration (Ratnovsky et al. 2008). Postural instability, as a common finding in people with HD (Brožová et al. 2011), may influence the smooth muscle contraction of the diaphragm and provide less mechanical stability from the abdominal muscles. The irregular breathing patterns seen in people with PD are thought to be due to central drive impairment (Seccombe et al. 2011), which is also a possibility in people with HD as mutant Huntingtin is present in the brainstem (Herndon et al. 2009). The loss of cells within the pons and medulla due to mutant Huntingtin may influence the generation of respiratory rhythm within the pre-Botzinger complex with consequent alteration of motor control of the diaphragm and intercostal muscles.

The findings of this study indicate that resistive load is increased in people with HD possibly due to laryngeal, pharyngeal and vocal cord dysfunction. These motor deficits may be as a consequence of striatal dysfunction, but may also be influenced by abnormal control of breathing swallow and speech within the brainstem. The irregular flow volume loops in people with manifest HD suggest an irregular breathing pattern which was first described by Leopold (1985) and Fischer et al. (1983).

Predisposition to type 2 hypercapnic respiratory as proposed in the conceptual framework of respiratory failure in people with HD is supported by the findings of this study. Although direct evidence of altered neural drive to respiration in people with HD was not gathered, data related to swallow dysfunction and irregular flow volume loops suggest that further research

is needed for a better understanding of the functional consequences of brainstem pathology. Strong evidence of decreased capacity of and increased load on the respiratory was found in people with manifest HD. The linear decline of respiratory function with disease progression indicates that signs and symptoms of respiratory dysfunction e.g. SNIP should be monitored alongside swallow and cough efficacy.

Linear decline of respiratory function with disease progression may also be secondary to the consequences of having a neurodegenerative condition e.g. decreased physical activity, exercise capacity and altered posture and these will be discussed in detail in the following section.

6.2.3 Variables influencing respiratory function in people with Huntington's disease

Relationships between respiratory function and exercise capacity, physical activity and posture were analysed. Those relationships with $R_s \geq 0.75$, indicating good to excellent correlation, were FVC and MIP with exercise capacity and physical activity, with MIP also having an excellent relationship with swallow capacity, see Figure 34.

Exercise capacity is dependent upon the integration of cardiovascular, neurological, respiratory and musculoskeletal function (Goldstein 1990). During exercise, CO_2 and metabolite production increases and homeostasis is maintained through chemoreceptor, baroreceptor and proprioceptive input, increasing the extrinsic load placed upon the respiratory system (Dempsey 2012). Measurement of exercise capacity encompasses a range of factors. This study identified that exercise capacity as measured by six minute walk distance, was less than previously noted in people with manifest HD: 173.32 ±166.133m compared to 381.66 ±129.97m in Quinn et al (2013). This may have been due to the average TFC in this study being 4.72, with people with manifest HD in the Quinn et al study having an average TFC of 8. Additionally, some of the participants in the Quinn et al study were based in a specialist unit which had a walking programme. Care must be taken in the comparison of these two studies as 17 of the participants in Quinn et al (2013) were also participants in the current study. Distance walked %predicted is reduced in people with pre-manifest HD, 78.63% ±12.84 and greatly reduced in people with manifest HD, 27.73% ±26.29 in this study.

The reduction in exercise capacity is greater than that seen in ALS, 65.2% ±17.4 predicted (Cheah et al. 2011) and MS, 62.8% ±27.8% predicted for total group, 74.3% ±23.2 for the mild disability subgroup and 40.2% ±21.8 for the moderate disability sub group (Wetzel et al.

2011). Distance walked in six minutes in people with mild to moderate PD (546 ±103) was found to be significantly less than in healthy control subjects (619 ±69) (Canning et al. 2006). The data in all the studies show increased variability which may be greater than in healthy cohorts. It has been suggested that disease specific reference equations should be used, as the variance in the data in people with PD was not fully accounted for by anthropometrics, gender and age as is found in healthy subjects. For people with PD, increased fall, balance and gender explained approximately 56.6% of the variance (Falvo and Earhart 2009). This is an important consideration when defining normal ranges, but for the current study the %predicted value gives a strong indication that exercise capacity is greatly reduced in people with manifest HD. Some of these differences between studies may be due to length of circuit, the current study circuit was 20m; the Wetzel et al study used 91.5m and 120m long corridors; Canning et al used a 30m walkway and Cheah et al did not report the circuit length. Although no difference has been shown in straight courses ranging from 15–50m (American Thoracic Society. 2002), turning may have more influence on distance walked in people with balance problems.

The excellent relationships between MIP and FVC and exercise capacity provide evidence of the link between underlying impairment within the respiratory system and functional ability. The relationship between 6MWD and MIP has also been noted in people with MS (Wetzel et al. 2011). Decreased inspiratory muscle strength leads to decreased FVC (De Troyer et al. 1980) and a restrictive respiratory pattern that can lead to hypoventilation (Simonds 2013). Increased elastic load on the respiratory system as measured by decreased FVC in this study, will result in an increased work of breathing (Bach and Kang 2000) which may influence the capacity to exercise. The decreased volume of air within the lung will reduce the minute ventilation and potentially reduce exercise capacity. This may relate to a reduced workload capacity in people with HD (Jones et al. 2012a) which is similar to findings in people with MS (Bosnak-Guclu et al. 2012) and PD (Canning et al. 2006), although the reasons for this diminished capacity are unknown.

Measures taken before and after the test indicate a normal physiological response to exercise i.e. slight rise in respiratory and heart rate, with no evidence of desaturation. Perceived dyspnoea ranged from nothing to slight (0-2) before the test and for some people increased to very severe, whilst others remained not breathless (range 0-7). Exertion was perceived differently to dyspnoea, with a range from no exertion to heavy exertion (6-15) before the test, increasing to very hard for some whilst others felt no exertion (6-17). This perception of

exertion before the test may be due to participants feeling exerted from the respiratory function tests that preceded the six minute walk test.

Physiological deficiencies may be compounded by biomechanical issues such as decreased gait velocity (Bilney et al. 2005), postural instability (Panzera et al. 2011) and decreased peripheral muscle strength (Busse et al. 2008) which will result in less distance being walked over a set time. Participants could use walking aids or support, if that was their normal walking behaviour and as such were as stable as possible and using a familiar pattern. Walking is a complex activity which requires cognitive planning and execution and in the context of a research study may require further cognitive processes to follow instructions. Motor planning deficit in people with HD is thought to be separate from motor symptoms (Giralt et al. 2012; Harrington et al. 2012) and this may have led to underperformance in this test.

When considering physical activity, people with HD had predominantly low levels of activity based on IPAQ scoring, the median score for people with pre-manifest HD (1502.50 (IQR=2418.4)) was within the moderate category and people with manifest HD (82.50 (IQR=618.8)) was in the low category. Direct comparisons with previous HD data are problematic as mean values were used, people with pre-manifest HD 2649 ±2107, people with manifest HD 1354 ±1796 (Quinn et al. 2013), but the people with manifest HD values in this study do appear much lower than Quinn et al (2013). The findings compare well to people with other neurodegenerative conditions. Physical activity as measured by IPAQ and accelerometers in people with MS is significantly reduced compared to matched healthy controls (Sandroff et al. 2012). Similarly, people with PD were found to be 29% less physically active compared to healthy control subjects and through regression methods inactivity was associated with worse walking performance, increased disability and greater disease severity and PD. These three variables accounted for only 24% of the variance and therefore many other factors may be associated with inactivity (van Nimwegen et al. 2011). Measuring physical activity is complex and although IPAQ demonstrates good reliability and validity (Helmerhorst et al. 2012; Khalil 2012; Quinn et al. 2013) the tool relies on memory and validity of the subject's answers, therefore caution must always be taken when interpreting findings. In particular, cognitive (Kingma et al. 2008) and memory (Paulsen et al. 2008) deficits may influence the measurement of physical activity via questionnaire in people with HD.

The relationship identified between respiratory function and physical activity is similar to that between respiratory function and exercise capacity; the ability to exercise potentially

influencing participation in physical activity. The relationship between decreased FEV_1 and physical inactivity has been demonstrated in a large cohort study, with suggested links between FEV_1 and morbidity and mortality (Jakes et al. 2002). Conversely, deconditioning due to disuse or inactivity will cause decreased muscle strength (Bortz 2005) which is related to respiratory muscle strength (Buchman et al. 2008). Cause and effect is thus unknown, however Buchman et al (2008) place respiratory muscle strength as the beginning of a causal chain which leads to reduced pulmonary function and death.

These inter-relationships are further confounded by social, cognitive and psychological factors. Social factors such as transport issues, expense, accessibility of leisure facilities and living in a rural community are additional barriers to people with long term health conditions (Smith et al. 2013). The support of health and fitness professionals as well as staff attitude is also seen as important factors supporting people with neurodegenerative conditions to engage in physical activity (The LIFE group 2011). In a qualitative study exploring client and therapists' views on exercise programmes (Quinn et al. 2010), people with HD and PD did not see that having the condition limited their ability to exercise and that it did not preclude them from attending a gym, but some felt that home exercises better suited their lifestyle. Therapists did however feel that cognitive impairment may affect the ability of a person with PD or HD to exercise independently. The ability to perform activities of daily living is influenced by both cognitive deficits (Peavy et al. 2010) and the inability to shift strategies for tasks (Giralt et al. 2012) which may make it difficult for people with HD to commence a new physical activity routine. From a behavioural perspective, Hamilton et al. (2003) suggests that profound apathy, lack of initiative and irritability may interfere with functional activities, even if the necessary motor and cognitive capacity is retained. Psychological issues such as distress, depression and anxiety may be either consequential to or integral to inactivity (Verbunt et al. 2003). Although these findings relate to people with chronic pain they may be transferable to people with HD due to the manifestation of depression as a symptom of HD (Estrada Sánchez et al. 2008). It is clear that the relationship between respiratory function and physical activity is multifactorial, with cause and effect relationships yet to be confirmed.

This study showed that people with manifest HD had a more kyphotic and chin down posture compared to people with pre-manifest HD. Thoracic angle demonstrated a moderate to good relationship with inspiratory muscle strength and a fair relationship with lung volume see Table 31. The data reflect decreases FVC seen in people with PD and camptocormia, defined

as an abnormal flexion of the thoracolumbar spine of ≥45º in upright standing (Marinelli et al. 2013) and people with kyphotic postures (Berdal et al. 2012; Harrison et al. 2007). The relationship between posture and respiratory function in HD was classified as moderate to good and is therefore different to the excellent relationships found between respiratory function and exercise capacity, physical activity and swallow capacity. This may be due to few participants having a fixed kyphosis (n=6, based on observations during assessment), and may be a consequence of the choreic nature of HD in the early stage of disease (Andre et al. 2010; Han et al. 2010).

A more slumped posture compresses internal organs (Lin et al. 2006) and reduces tidal volume and minute volume (Landers et al. 2003) which may explain the relationship between increased thoracic curve and decreased FVC in this study. The relationship with respiratory muscle strength is likely to be due to altered biomechanics in the slumped position. A slumped position induces changes in chest wall diameter in all planes, which influences rib cage compliance and alters the anatomical position of respiratory muscles. The chin down position will alter the length of scalene and sternocleidomastoid, with the increased thoracic curve altering external intercostal and parasternal muscle length with consequent reduction in pump handle movement (Lee et al. 2010). Decreased spinal mobility and chest wall compliance contribute to decreased lung volumes in people with kyphosis (Berdal et al. 2012) with the postural changes likely to cause altered biomechanics and efficacy of the respiratory muscles. These findings indicate that posture is an influencing factor in increasing elastic load and decreasing capacity of the respiratory muscle pump.

6.2.4 Respiratory function and progression of Huntington's disease

This study provides new information that the decline in respiratory function in people with HD is linear, rather than being a specific problem of the late stage and that therapeutic intervention may be necessary at the middle stage of the condition. All measures of respiratory function, except FEV_1/FVC, demonstrated significant relationships with functional capability as measured by TFC and motor impairment as measured by UHDRS:TMS in that respiratory function decreased as HD progressed, see Table 37 and Table 38. The scatterplots for TFC and TMS were similar for each respiratory variable and were also similar between absolute respiratory scores and %predicted scores.

Scatterplots for FVC, FVC%predicted, PCF, MIP, MIP%predicted and SNIP were all similar in terms of scatter around the line of best fit, with points scattered similarly throughout the range of TFC. FEV_1 and FEV_1%predicted demonstrated more scatter, but still had R_s values

of 0.805 and 0.827 respectively. The scatterplot for SMIP was dissimilar to other measures of respiratory function, with more dispersion of plots when TFC >8.

The scatterplot of PCF and TFC, with reference lines for 270L/min and 160L/min, suggests that 46.3% (n=19) of people with manifest HD need supportive management strategies for cough and 24.4% (n=10) have an ineffective cough based on physiotherapy guidelines (Bott et al. 2009). Of the 10 people who had ineffective cough, three had a PEG tube fitted and six reported having swallow problems necessitating special food preparation. One person reported that they had no difficulties with swallowing. From the linear regression equation (PCF=120.36+27.91TFC), when PCF is 270L/min, TFC is 5.36. This has important clinical implications in that PCF should be monitored regularly and in particular when TFC <6 in order to implement strategies that could increase inspiratory capacity and expiratory flow e.g. maximal insufflation/exsufflation (Chatwin et al.2003) or expiratory muscle training (Gosselink et al. 2000). It must be noted that the measures of cough in this study were volitional and may differ from a reflex cough. In other words, participants who produced PCF < 160L/min voluntarily may be able to produce higher values if the integrity of the airway is challenged during feeding or drinking. The neural control of breathing, cough and swallow is integrated and complex (Davenport et al. 2011) and it is therefore difficult to deconstruct reflex and voluntary cough in order to explore this possibility. Additionally, assessment of reflex cough is not recommended in people with neurodegenerative conditions due to lack of evidence (Hammond and Goldstein 2006). The physiotherapy guidelines, however, use best available evidence for its recommendations regarding strategies for people with PCF <270L/min.

The decline in respiratory function throughout the progression of manifest HD is not solely attributable to the ageing process as %predicted values showed similar relationships with TFC and UHDRS:TMS as did absolute values. These findings are similar to those in people with late stage MS, with the extended disability status scale showing significant correlations with FVC% predicted ($r=0.87$, $p<0.001$); MEP% predicted ($r=0.79$, $p<0.001$) and cough efficacy ($r=0.45$, $p<0.05$) (Gosselink et al. 2000). The relationship between respiratory function and disease severity was not found in people with mild to moderate MS (Foglio et al. 1994; Koseoglu et al. 2006). Although the overall findings of the observation study were that respiratory function declines with disease progression, the time gap of approximately 15 months in the follow up sub-study was not sufficient to show significant change in respiratory function over time. The progressive decline in respiratory function with age (Lalley 2013) was addressed by using %predicted values, which did show average percentage decrease in

FVC% predicted of 1.85% and MIP% predicted of 19.68%, however MEP% predicted increased by 5.41%. These results may be unsurprising in terms of progression of HD, the rate of decline being 0.44 TFC units per year (Meyer et al. 2012) and life expectancy of 15-20 years from onset of symptoms (Bates 2005).

The findings of linear decline were unexpected, but indicate that prognostic indicators could be used to identify patients at risk of respiratory failure. In relation to acute type 1 hypoxaemic respiratory failure, PCF would indicate those with values < 270L/minute who require strategies to increase inspiratory capacity and expiratory flow in order to effectively clear secretions. Measurement of FVC would indicate decreasing lung volume that could lead to hypoventilation and progressively increase load on the respiratory pump. As for people with ALS, an FVC of <80%predicted should be further investigated in terms of nocturnal desaturation and potential use of non-invasive ventilation (Anderson et al. 2012). Declining capacity of the respiratory pump as measured by SNIP would indicate potential type 2 hypercapnic respiratory failure which could be further investigated through blood gas analysis.

6.3 Conclusions from observation study

A conceptual framework of respiratory failure in people with HD provided the rationale and methodological basis for the observation study of respiratory function in people with HD. The theoretical postulations were based on existing knowledge of pathological changes in HD and supported by evidence regarding respiratory function in people with PD, MS and MND/ALS. The key findings of decreased lung volume, impaired swallow and decreased cough efficacy support the theory that people with HD are susceptible to type 1 hypoxaemic respiratory failure. Further research is required to quantify the frequency of aspiration pneumonia in people with HD and describe current management strategies. Progressive decline in lung volume will increase the elastic load placed on the respiratory pump and with concomitant increased resistive load and decreased capacity predispose people with HD to type 2 hypercapnic respiratory failure. The exact causes of the underlying respiratory dysfunction are as yet unknown as further research is needed to explore whether HD pathology is primarily involved and how factors such as decreased exercise capacity, physical activity and altered posture impact on respiratory function. These findings are illustrated in Figures 41-43.

The functional problems associated with these findings are decreased ventilatory capacity, decreased respiratory muscle strength and decreased cough efficacy leading to retention of secretions. It has been suggested that the key factor of respiratory failure in people with neurodegenerative conditions is respiratory muscle weakness (Benditt and Boitano 2013; Buyse 2006) as this impacts on inspiratory capacity and cough efficacy. Based on the findings from the observation study an intervention study was planned to explore the feasibility and benefit of a physiotherapy technique to improve respiratory function and potentially reduce the risk of respiratory failure. The following chapters of this thesis will report the findings of a systematic review of physiotherapy management of respiratory problems in people with neurodegenerative conditions and the rationale, methods and results of the intervention study.

Figure 41 Theoretical causes of type 1 hypoxaemic respiratory failure in people with Huntington's disease

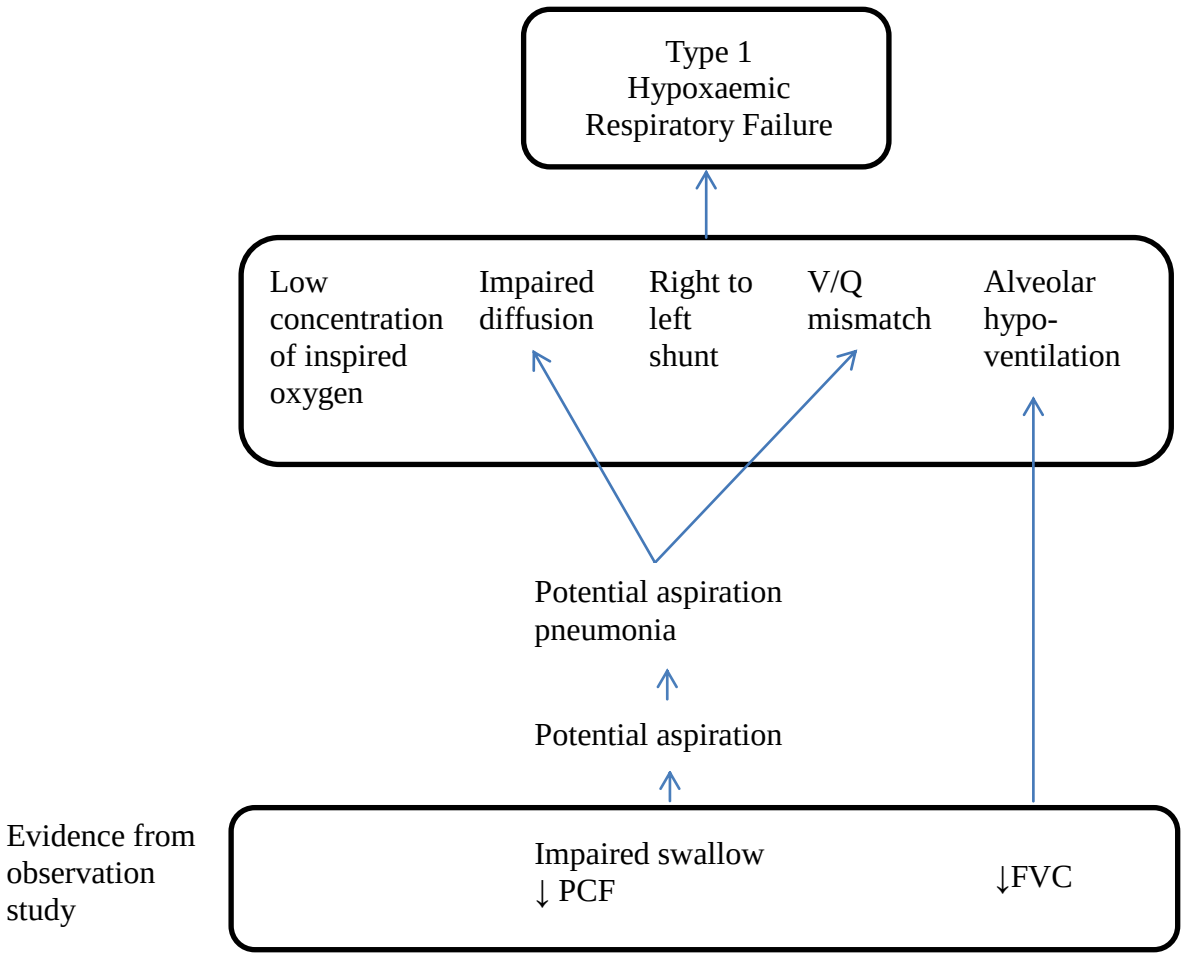


Figure 42 **Theoretical causes of type 2 hypercapnic respiratory failure in people with Huntington's disease**

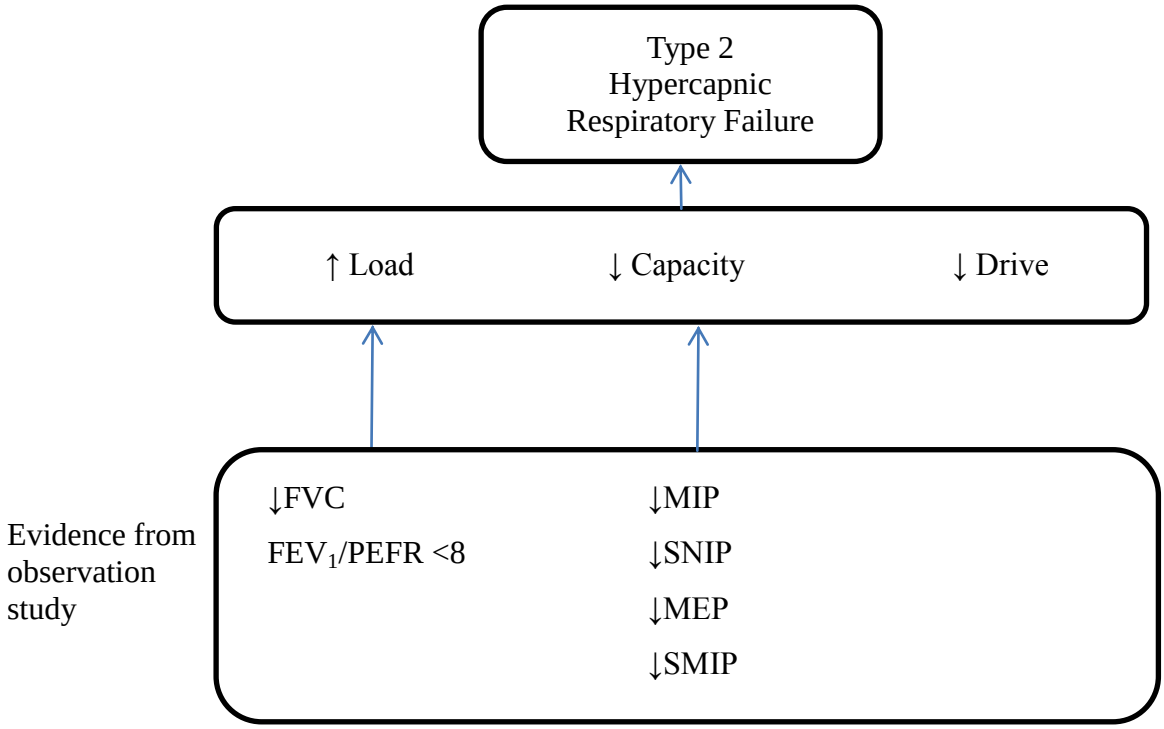
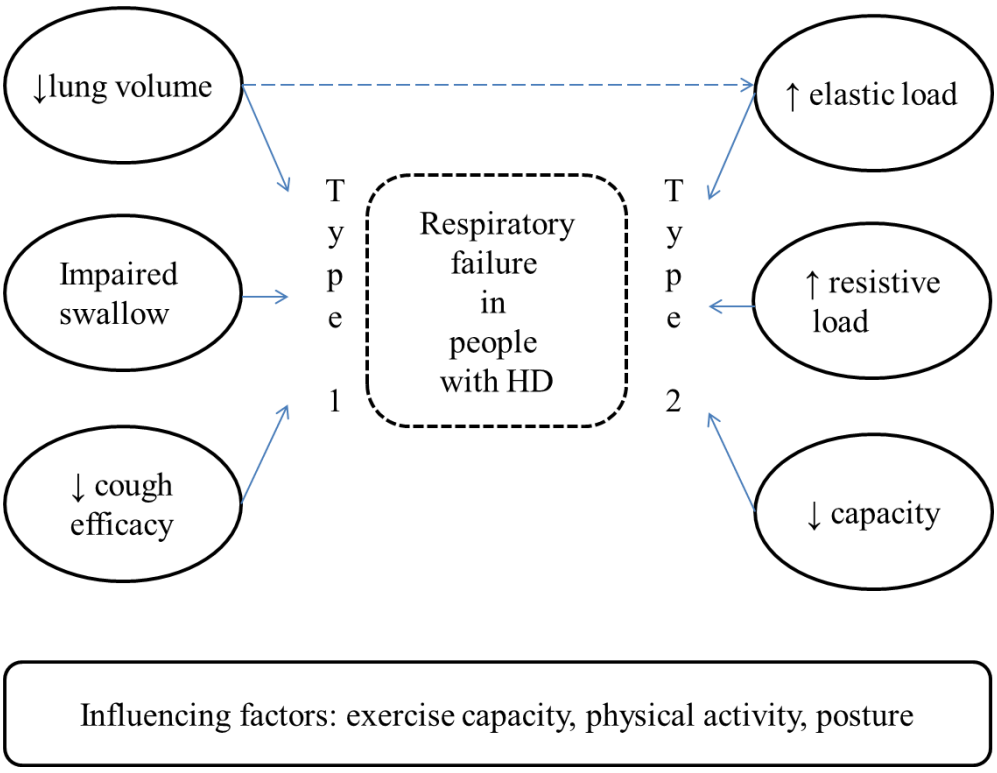


Figure 43 **A model of respiratory failure in people with Huntington's disease**



7 Intervention study: Literature Review

7.1 Introduction

The main findings from the observation study suggest that people with manifest HD may have functional problems of retained secretions, decreased ventilation and decreased capacity of the respiratory muscle pump due to underlying respiratory dysfunction. Physiotherapy management of these problems was reviewed in order to identify an intervention for people with HD that could improve respiratory function and potentially decrease the likelihood of respiratory failure. When the intervention study was developed, little was known regarding management of respiratory problems in people with HD; a qualitative study identified that respiratory therapy was used by physiotherapists in the United Kingdom, but detail of specific interventions were not provided (Busse 2008). It was therefore necessary to review the literature related to people with PD, MS and MND/ALS. The specific question to be answered in the review was 'how do physiotherapy interventions for retained secretions, decreased lung volume and decreased capacity of the respiratory pump in people with neurodegenerative conditions influence respiratory function'. The three functional problems were then used to provide the structure for the review. The exploration in this thesis was specific to respiratory function; therefore the review only included studies with outcomes measures of respiratory function.

7.2 Search Strategy: Physiotherapy management of respiratory problems

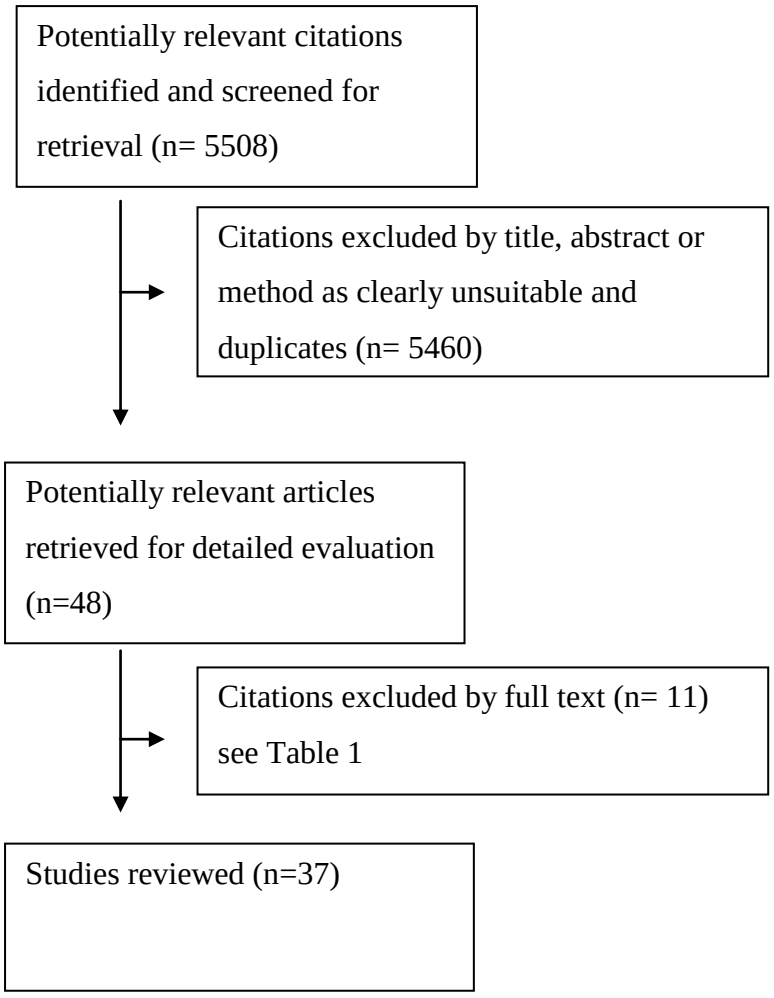
The search was limited to English language articles found using the following databases: Medline, EMBASE, AMED, CINAHL, HUGEnet, British Library Direct and SIGLE from inception to September 2013. A participant, intervention, comparison, outcome (PICO) approach (The Joanna Briggs Institute. 2008) was used to generate key words for all searches. Literature was appraised using the critical appraisal skills programme (CASP) (Critical Appraisal Skills Programme. 2007) guidance. Bibliographies of all relevant studies and reviews were searched by hand. References were managed through EndNote version X5. Population keywords included 'neuro*', 'Parkinson's disease', 'Amyotrophic Lateral Sclerosis', 'Motor Neurone Disease', 'Multiple Sclerosis', and 'Huntington's disease'. Intervention keywords included 'physiotherapy' and 'respiratory' with outcome words including 'lung'. Subsequent to the initial search and analysis of the categories of evidence found, two further search terms were used; 'respiratory muscle strength' and 'retained secretions', see Figure 44 and Figure 45 for a summary of the search strategy and record of findings.

Exclusion criteria were: the population consisted entirely of neuromuscular conditions such as myasthenia gravis and muscular dystrophies; all subjects <18 years old; subjects not breathing spontaneously; the intervention did not measure respiratory function; n<2.

Figure 44 Summary of search strategy:

1 = physiother*
2 = neuro*
3 = respir*
4 = lung
5 = respiratory muscle strength
6 = retained secretions
7 = 3 OR 4 OR 5 OR 6
8 = 1 AND 2 AND 7
9 = motor neurone disease
10 = amyotrophic lateral sclerosis
11 = multiple sclerosis
12 = Huntington's disease
13 = Parkinsons disease
14 = 9 OR 10 OR 11 OR 12 OR 13
15 = 14 AND 7

Figure 45 Flow diagram for selection of studies



Details of individual studies are in Tables 41-44 with critical appraisal in Appendix 6.

7.3 Management of retained secretions

7.3.1 Description of techniques to manage retained secretions

Cough efficacy, which is determined by respiratory muscle strength and glottic function, has been highlighted as functionally impaired in people with neurodegenerative conditions (Benditt and Boitano 2013) and therefore may result in retention of secretions during respiratory infections. Aspiration pneumonia is common in people with neurodegenerative conditions (Heemskerk and Roos 2010; Lalmohamed et al. 2012; Rafiq et al. 2012; Williams-Gray et al. 2013) and thus effective ways of managing retained secretions in people with neurodegenerative conditions need to be identified to enhance clinical practice.

Physiotherapy techniques to manage retained secretions include: active cycle of breathing technique (ACBT); autogenic drainage; postural drainage; manual techniques such as percussion and vibrations; positive expiratory pressure devices; high frequency chest wall oscillation; assisted cough and mechanical insufflation-exsufflation.

ACBT, as described by Webber (1990), is a cycle of breathing control, thoracic expansion exercise and the forced expiratory technique (FET). Breathing control is relaxed breathing at tidal volume at the patient's own rate and depth and is used interspersed between thoracic expansions and FET. Thoracic expansion exercises are breaths at higher than tidal volumes which aim to increase lung volume by increasing the flow of air through collateral ventilation pathways at alveolar level and mobilise secretions in the alveoli (Button and Button 2013). FET is a forced expiration with an open glottis creating dynamic compression of the airway. Downstream i.e. toward the mouth, of the compression very high airflows clear mucus from the airway walls (Selsby and Jones 1990). Airway clearance techniques are effective in the short term in the management of excess mucus in people with cystic fibrosis (Van der Schans et al. 2000) but there is insufficient evidence to promote the use of ACBT over other techniques (Robinson et al. 2010). For individual patients there are no objective markers to endorse particular use of a technique, with adherence dependent upon individual preference (Pryor et al. 2010). ACBT is recommended in cystic fibrosis (CF) and bronchiectasis at grade A (at least one meta-analysis) and components such as breathing exercises are recommended for people with: spinal cord injury, grade D (expert opinion, case reports); Asthma, grade A; chronic obstructive pulmonary disease (COPD), grade D (Bott et al. 2009).

Autogenic drainage focuses on breathing exercises at different lung volumes. Breathing is a slow inspiration with 2-4 second hold and a sighing expiration. When these breaths are used at low lung volumes, secretions are mobilised in the peripheral airways which then collect in the middle airways at mid lung volumes. Evacuation or expectoration then occurs when breathing at high lung volumes (Chevaillier 2009). Evidence on the effectiveness of autogenic drainage is limited but is recommended at grade A for people with CF and at grade D for COPD (Bott et al. 2009).

CF and non-CF bronchiectasis result in large quantities of thick sticky secretions which often require the assistance of gravity to help drain secretions. Postural drainage uses knowledge of broncho-pulmonary anatomy (The Thoracic Society. 1950) to position the thorax in a way that will allow gravity to have best effect on secretions, causing them to move from peripheral to central airways to be expectorated. The recommendation of postural drainage

for CF and bronchiectasis is grade B (high quality systematic review) and should only be used if safe in COPD and can further add to clearance, grade D.

Manual techniques such as percussion and vibrations may be used in conjunction with ACBT and postural drainage. Percussion is thought to loosen secretions from bronchial walls and vibrations increase expiratory flow rate in the peripheral and central airways (Wong et al. 2003) thus enabling secretions to be moved from peripheral and central airways and expectorated. Percussion and vibration techniques are thought of as 'conventional' physiotherapy and with few studies investigating their efficacy, specific recommendations for use cannot be made (Bott et al. 2009). When percussion and vibration are combined with postural drainage, this chest physiotherapy is recommended in people with CF at grade C (McCool 2006b).

A development of manual vibrations is high frequency chest wall oscillation (HFCWO), which uses a vest connected to an air pulse generator and provides compression of the chest at frequencies of 5-20Hz (Button and Button 2013) Although HFCWO has cost implications, it is recommended, in people with CF, grade A (Bott et al. 2009). Smaller devices such as positive expiratory pressure (PEP) and oscillating PEP devices are also recommended for people with CF and non-CF bronchiectasis, grade A (Bott et al. 2009). These devices provide between 5-20cmH_2O pressure on expiration which is thought to maintain airway patency, promote airflow to obstructed airways and thus enhance clearance of secretions (Mortensen et al. 1991).

In physiotherapy practice, expectoration of retained secretions may be managed by improving the cough effectiveness. Cough effectiveness can be improved by increasing inspiratory volumes through maximal insufflation and breath stacking (McCool 2006b), by enhancing forced expiration by means of maximal exsufflation and manually assisted techniques and by manually assisted cough. These interventions can be applied to people who are self-ventilating and those who are ventilated by invasive and non-invasive means.

Assisted cough and mechanical insufflation-exsufflation are techniques that aim to assist the expectoration of secretions when cough may be ineffective and therefore are recommended for people with spinal cord injury and people with neuromuscular disorders, both at grade D (Bott et al. 2009). Assisted cough is a manual technique performed on a person by applying an inward and upward force against the thorax, as a substitute for abdominal and intercostal muscle work (Harris and Ward 2008). A mechanical insufflation-exsufflation device promotes maximal lung inflation through application of positive pressure via a face mask followed by a rapid negative pressure which imitates flow changes occurring during a cough.

It is thought that this enforced cough would enable clearance of secretion (Chatwin et al. 2003). A mechanical glottis, an external device which mimics the normal closure of the glottis, has also been used to enhance cough (Suleman et al. 2004).
The physiotherapy techniques described above have some theoretical underpinning and variable efficacy in the management of retained secretions. Further analysis of evidence was carried out in people with neurodegenerative conditions. This evidence was collected and analysed systematically, see Appendix 6 for critical analysis.

7.3.2 Management of retained secretions in people with neurodegenerative conditions

Ten studies were selected that described treatment/intervention for retained secretions, see Table 41 for details of the studies. All individual studies were small, populations were ALS/MND (n=6) but did include other neurodegenerative conditions (n=4). No studies were randomised controlled trials and interventions were not standardised across studies. Outcomes for cough effectiveness studies were consistent; measuring expiratory flow rates. Three studies used high frequency chest wall oscillation as an intervention to mobilise secretions and one study investigated mechanical glottis to enhance cough. Six studies compared combinations of increasing maximal insufflation capacity, maximum insufflation-exsufflation and manually assisted cough. The primary outcome measure for most studies (7/10) was peak cough flow (PCF) with two using peak expiratory flow rate (PEFR) and one using forced vital capacity (FVC) and oxygen saturation (SaO_2). PCF is the maximal flow rate from a cough manoeuvre and differs from PEFR in that the manoeuvre follows a closed rather than open glottis. A critical cut off point for effective cough has been established as PCF $\geq$ 160L/min (Bach et al.1998).

7.3.3 Studies related to mobilisation of secretions

High frequency chest wall oscillation was the only modality with evidence for use in people with neurodegenerative conditions. In three studies with a total of 62 patients with ALS, high frequency chest wall oscillation was applied twice a day for between 10-30 minutes per session (Chaisson et al. 2006; Jackson et al. 2006; Lange et al. 2006). Although there were no significant changes in respiratory function (S_aO_2, FVC, PCF), breathlessness decreased significantly (Lange et al. 2006) and 92% felt better after treatment (Jackson et al. 2006). Based on this evidence, high frequency chest wall oscillation may enhance mobilisation of secretions in people with neurodegenerative conditions, but large scale studies are necessary to provide conclusive findings.

7.3.4 Studies related to improvement of cough effectiveness

Winck et al (2004) investigated the effects of sequentially increasing mechanical insufflation-exsufflation pressures from ±15cmH_2O to ±30 and then to ±40cmH_2O on parameters including PCF, SaO_2, and dyspnoea. The sample group included 13 subjects with ALS and 7 subjects with other neurodegenerative conditions. PCF and SaO_2 measured at baseline and after mechanical insufflation-exsufflation of ±40cmH_2O showed significant improvement in subjects with ALS ($p<0.005$ PCF and SaO_2) and those with neurodegenerative conditions (PCF $p<0.05$, SaO_2 $p<0.005$). Dyspnoea was measured in just the neurodegenerative conditions group and significantly decreased from baseline to ±40cmH_2O ($p <0.05$). Median PCF increased from 180L/min to 220L/min in the ALS group and from 170L/min to 200L/min in the neurodegenerative conditions group. These are clinically significant results as both groups improved their ability to independently clear secretions as shown by median values > 160L/min.

Bach (1993), Chatwin et al (2003) Mustfa et al (2003) and Sancho et al (2004) all compared combinations of mechanical insufflation-exsufflation, manual assisted cough and breath stacking in people with ALS and neurodegenerative conditions using PCF as one of the outcome measures. For patients with ALS (n=73, (Mustfa et al. 2003; Sancho et al. 2004), mechanical insufflation-exsufflation was found to be more effective than manually assisted cough and unassisted cough in those patients without bulbar involvement and who are stable. Mechanical insufflation-exsufflation was not effective in those with little lung function impairment and those with bulbar dysfunction who also had a maximal inspiratory capacity of >1 litre and a PCF (generated from maximal insufflations) of <162L/min, probably due to upper airway collapse during expiration. The specific issue of bulbar involvement highlights the importance of impaired cough due to upper airway weakness which may not be overcome by these interventions (Mustfa et al. 2003). In people with neurodegenerative conditions Bach (1993) found that mechanical insufflation-exsufflation was more effective than manually assisted cough with breath stacking; cough with insufflations and unassisted cough. Slightly different results were found by Chatwin et al (2003) who found that although mechanical insufflation-exsufflation and exsufflation alone were better than unassisted cough, they were not significantly better than assisted cough. This study used a mixed adult and child sample. The evidence from these studies indicates that mechanical insufflation-exsufflation is effective in producing sufficient volumes for effective cough in people with neurodegenerative conditions that have impaired lung function. In a small study of 10

patients with neurodegenerative conditions, Trebbia et al (2005) found that a combination of manually assisted cough and manual hyperinflation significantly improved PCF.
An alternative aid to cough may be a mechanical glottis device that can imitate glottis closure and thus potentially generate pressures that produce adequate PCF. Suleman et al (2004) investigated the use of such a device in healthy controls and people with bulbar problems and demonstrated that the device created a PEFR significantly higher than that of both a straightforward PEFR manoeuvre and a cough manoeuvre in patients. In the healthy control group PEFR was highest with a cough manoeuvre and lowest with normal PEFR manoeuvre.

Physiotherapy based interventions to improve cough effectiveness by increasing PCF appear to have some efficacy for people with neurodegenerative conditions. Mechanical insufflation-exsufflation and manually assisted cough appear to be more effective than unassisted cough (Bach 1993; Chatwin et al. 2003; Mustfa et al. 2003). The choice of physiotherapy intervention depends upon the patient's vital capacity (Sancho et al. 2004) and whether the patient is stable and needs to maintain clear airways or has an acute respiratory infection and needs to clear secretions. Skills in manually assisted cough and maximal insufflation-exsufflation can be taught to carers and therefore may be suitable within the primary care setting. The heterogeneous populations used including neurodegenerative and neuromuscular disorders make it difficult to draw conclusions for specific disease populations.

Table 41 Studies related to retained secretions

Study	Population	Intervention and comparison	Key significant findings
Bach 1993	21 people with neurodegenerative conditions	Single group, comparison of PCF during: A unassisted cough, B unassisted cough preceded by breath stacking C manually assisted cough preceded by breath stacking D mechanical insufflation-exsufflation (several 5 cycle applications at comfortable pressures)	PCF in D>C p <0.0005 PCF in C>B p <0.001 PCF in B>A p <0.0005
Chatwin et al 2003	21 adult and child with neurodegenerative conditions	Single group, comparison of PCF during: A unassisted cough B physiotherapy assisted cough C non-invasive ventilator assisted cough D exsufflation assisted cough E insufflation-exsufflation assisted cough	PCF in E>D p <0.001
Chaisson et al 2006	9 ALS	2 groups, comparison of FVC in: A standard care plus high frequency chest wall oscillation applied for 15min, twice daily B standard care Both groups received instruction on cough augmentation manoeuvres	No difference in rate of decline in FVC between high frequency chest wall oscillation and standard treatment

Study	Population	Intervention and comparison	Key significant findings
Jackson et al 2006	18 ALS	Retrospective analysis of FVC, MIP, and PCF before and after high frequency chest wall oscillation, applied twice daily for 10-20 minutes or more frequently if needed. Frequency = 10-14Hz, pressures 30–40cmH_2O	No significant differences
Lange et al 2006	46 ALS	Randomised control trial, outcome measures: FVC predicted and PCF A high frequency chest wall oscillation, twice daily for 10-15 minutes, for 12 weeks. Frequency = 10-12Hz, pressures 1-4 (linear scale no units) B Control no treatment.	A & B No change in FVC or PCF Sub analysis of patients with 40<FVC<70% predicted, showed FVC significantly decreased in B but not A.
Mustfa et al 2003	47 ALS	Single group comparison of PCF during: A unassisted cough B manual assisted cough C exsufflation assisted cough D insufflation assisted cough E insufflation/exsufflation assisted cough	PCF in C > A, B, D, E $p<0.01$
Sancho et al 2004	26 ALS	Single group, comparison of PCF during: A maximal insufflation assisted cough B maximal insufflation-exsufflation assisted cough Mechanical insufflation-exsufflation delivered at ± 40cm H_2O	Mechanical insufflation-exsufflation can increase PCF in stable patients with ALS with 2.7L/s < PCF_{MIC} <4L/s ($_{MIC}$ at maximal insufflation capacity)

Study	Population	Intervention and comparison	Key significant findings
Suleman et al 2004	10 MND	Single group, comparison of PEFR in: A PEFR B PEFR with mechanical glottis C PEFR with cough	PEFR in B>A $p<0.005$ PEFR in C>A $p<0.005$ PEFR in C>B $p<0.005$
Trebbia et al 2005	10 people with neurodegenerative conditions	Single group, comparison of PCF in: A unassisted cough B manually assisted cough C mechanical insufflation D manually assisted cough and mechanical insufflation	PCF in B, C, D>A $p<0.01$ PCF in D>C, B $p<0.01$
Winke et al 2004	13 ALS 7 people with other neurodegenerative conditions	Single group, comparison of PCF, SaO_2, dyspnoea in: A baseline B MIE ±15cmH_2O C MIE ±30cmH_2O D MIE ±40cmH_2O	ALS PCF in D>A $p<0.005$ SaO_2 in D>A $p<0.005$ Other neurodegenerative conditions PCF in D>A $p<0.05$ SaO_2 in D>A $p<0.005$ Dyspnoea in D>A $p<0.05$

Key to Table 41

ALS	Amyotrophic lateral sclerosis
FVC	Forced vital capacity
MIE	Maximal insufflation exsufflation
MIP	Maximal inspiratory pressure
PCF	Peak cough flow
PEFR	Peak expiratory flow rate
S_aO_2	Saturation of oxygen

7.4 Management of decreased lung volume

Atelectasis leading to decreased lung volume may represent an underlying cause of type 1 hypoxaemic respiratory failure which may lead to type 2 hypercapnic respiratory failure. Decreased lung volume has been demonstrated in people with PD and management of this problem may decrease the likelihood of progressive atelectasis.

7.4.1 Description of techniques to manage decreased lung volume

Physiotherapy techniques to increase lung volume include thoracic expansion exercises; positioning and postural advice and general exercise. As described in Section 7.3, thoracic expansion exercises can increase lung volume by utilising collateral ventilation between alveoli (Button and Button 2013). The technique of positioning to improve lung volume is based upon the effect of gravity on ventilation throughout the lung. At tidal volume breathing, ventilation is greater in dependent regions of the lung compared to non-dependent regions. This is due to the effect of gravity on lung structure, causing intra-pleural pressure to be more positive in dependent regions, causing compression of alveoli which are thus more compliant during inspiration. (Bryan et al. 1966). This deformation of the lung tissue under its own weight also influences pulmonary perfusion, in that non-dependent regions will contain fewer blood vessels than dependent regions (Hopkins et al. 2007). Matching of ventilation and perfusion is necessary for optimal pulmonary function and physiotherapists use this knowledge to position people who have regional dysfunction of ventilation (Dean 1985). Gross changes in posture also influence pulmonary function in terms of lung volume. Changing posture from upright sitting through to supine lying shows a decrease in rib cage movement and consequent decreases in tidal volume and minute ventilation (Romei et al. 2010). Similarly, kyphotic postures reduce vital capacity (Harrison et al. 2007). Physiotherapy management aims to optimise lung volumes by either passively positioning people who are unable to position themselves and/or educating carers and patients regarding best positions for respiratory function. Postural alignment and appropriate seating is

recommended for people with HD in order to maximise functional ability and to reduce the risk of aspiration and respiratory complications (Quinn and Busse 2012).

Exercise influences breathing mechanics as the respiratory system strives to maintain homeostasis. During exercise, tidal volume and breathing frequency increase to improve gaseous exchange (Dominelli and Sheel 2012). Increased tidal volume is thought to be predominant in low intensity exercise, with breathing rate increasing with more intense exercise. The initial increase in tidal volume is due to optimal diaphragmatic contraction as a consequence of stretch, as end expiratory volume decreases due to active expiration (Babb 2013). Exercise to improve cardiorespiratory function is recommended in asthma (Grade B); cystic fibrosis (Grade B); spinal cord injury (Grade D) and as part of pulmonary rehabilitation for people with COPD (Grade A) (Bott et al. 2009).

7.4.2 Management of decreased lung volume in people with neurodegenerative conditions

Studies related to increasing lung volume in people with neurodegenerative conditions included general exercise and specific breathing exercises. Seven studies were found that investigated the influence of different types of exercise in people with neurodegenerative conditions, see Table 42. Three studies (n=168 people with MS) (Mostert and Kesselring 2002; Rampello et al. 2007; Rasova et al. 2006) compared bike training with neurological rehabilitation with positive changes in FVC found in two studies (Mostert and Kesserling 2002; Rasova et al. 2006). The lack of positive findings in Rampello et al. (2007) may have been due to small numbers, as after dropouts only five subjects remained in each group. Another small study (n=9) in people with PD demonstrated no difference in respiratory function after a specific pulmonary rehabilitation program although the negative finding may also have been due to the mean value for predicted FVC being in the normal range (107.11%) (Koseoglu et al. 1997).

The study on diaphragmatic training in people with ALS (n=8) (Nardin et al. 2008) used the principle of decreasing end expiratory volume in order to maximise the length tension relationship of the diaphragm in order to enhance diaphragm contraction. There were no changes in FVC after the intervention which may indicate that any change in lung volume is temporary whilst performing the exercise.

In contrast, an intervention of deep breathing exercises in 24 people with PD demonstrated significant increases in FVC, FEV_1, PEFR and maximal voluntary ventilation (MVV) (Genç et al. 2012). In this study, the subjects' % predicted FVC was 83.62 ±16.09 which may

indicate the potential for improvement. The intervention differed from Nardin et al. (2008) in that slow deep breaths with end inspiratory hold were included. These exercises aim to increase airflow through collateral ventilation and therefore may have expanded previously collapsed alveoli, thus increasing FVC.

A positive trend in change of FVC and MEP was seen following an intervention of breathing enhanced upper extremity exercises in people with MS (n=40) (Mutluay et al. 2007). These exercises targeted accessory muscles, but as FVC % predicted was not in a pathological range (91±17) it is unlikely that accessory muscles are used in normal breathing, therefore limiting the efficacy of the intervention.

Table 42 Studies related to exercise

Study	Population	Intervention and comparison	Key significant findings
Genç et al 2012	24 PD	Single group, comparison of FEV_1, FVC, FEV_1/FVC, PEFR, MVV pre and post intervention Deep breathing exercises 3 x 15 daily for 12 weeks	FVC, FEV1, PEFR significant improvement $p<0.001$ MVV significant improvement $p<0.006$ FEV1/FVC no change
Koseoglu et al 1997	9 PD	Single group comparison of FEV_1, FVC, PEFR, MVV, VC, pre and post intervention Pulmonary Rehabilitation including specific breathing exercises 60 minutes, 3 days/week for 5 weeks.	No significant differences pre and post in any variable
Mostert and Kasserling 2002	37 MS, 26 healthy control	4 groups, comparison of FEV_1, FVC, FEV_1/FVC, PEFR, MVV A MS exercise training (bike) B MS control, normal physiotherapy C Healthy control, no regular physical exercise D Healthy control, exercise training (bike) Exercise training: 30 minutes, 5 times/week for 3-4 weeks, individualised intensity.	A ↑ FVC, PEFR $p<0.05$ B ↑ PEFR $p<0.05$

Study	Population	Intervention and comparison	Key significant findings
Mutluay et al 2007	40 MS	2 groups, comparison of FEV_1, FVC, FEV_1/FVC, MIP, MEP A Breathing enhanced upper extremity exercises B Control no intervention Breathing exercises programme 30 minutes, once/day for 6 weeks	A ↑FEV_1, FEV_1/FVC compared to B
Nardin et al 2008	8 ALS	Single group, comparison of FVC, hypercapnic ventilatory response, breathing pattern pre and post intervention Diaphragmatic training: 5 sets of 10 minutes daily for 12 weeks	No change in FVC, hypercapnic ventilatory response. 4/8 altered breathing pattern
Rampello et al 2007	19 MS	Single group, cross over design, comparison of FEV_1, FEV_1/FVC, VC, MIP, MEP A Aerobic training (cycle ergometer) B Neurological rehabilitation Training 55 minutes, 3 times/week for 8 weeks. Intensity dependent on work rate and increased to 80% maximum work rate Rehabilitation 60 minutes, 3 times/week for 8 weeks.	No difference in lung function

Study	Population	Intervention and comparison	Key significant findings
Rasova et al 2006	112 MS	4 groups, comparison of FEV_1, FVC, PEFR A Neurophysiological physiotherapy B Aerobic bike training C Combined A & B D Control Physiotherapy 1 hour, twice/week for 2 months Bike training twice/week, intensity 60% maximal oxygen uptake, time dependent on disability score range 10-30 minutes Mixed training 1 hour twice/week physiotherapy and bike training as above. Control – no intervention.	B ↑FVC $p<0.05$

Key to Table 42

PD	Parkinsons disease	PEFR	Peak expiratory flow rate
MS	Multiple Sclerosis	MVV	Maximal voluntary ventilation
ALS	Amyotrophic lateral sclerosis	MIP	Maximal inspiratory pressure
FEV_1	Forced expiratory volume in 1 second	MEP	Maximal expiratory pressure
FVC	Forced vital capacity	VC	Vital capacity
FEV_1/FVC	Forced expiratory volume in 1 second/ Forced vital capacity ratio		

7.5 Management of decreased capacity

Ventilatory function is determined by inspiratory muscle strength with functional impairment being observed as nocturnal and daytime hypoventilation (Benditt and Boitano 2013). Two main interventions were identified to address the problem of respiratory muscle weakness; non-invasive ventilation (NIV) and respiratory muscle training. NIV aims to reduce the work of breathing and conserve energy whilst respiratory muscle training aims to strengthen inspiratory and expiratory muscles and improve endurance. Studies on the effectiveness of these interventions include a systematic review including eight randomised control trials, five additional randomised controlled trials, five prospective observational studies, two retrospective observational studies and six experimental studies; see Table 43 and Table 44 for details. Further detail on respiratory muscle training can be found in the next section.

7.5.1 Non-invasive ventilation

Non-invasive ventilation can be administered via nasal mask, mouthpiece or oro-nasal masks and can be volume cycled, pressure cycled or Bi level positive airway pressure (BiPAP) (Annane et al. 2009). Ten studies were selected that involved non-invasive ventilation as an intervention, see Table 43. One was a systematic review with a specific population of ALS. Other studies selected that were not contained within the review included 391 people with ALS and 68 mixed population studies. The studies were mainly prospective observational studies (n= 5), with two retrospective studies and two experimental studies. Interventions included BiPAP, volume cycled NIV and pressure cycled NIV. Outcome measures included FVC, SNIP, MIP, MEP, lung compliance and Tlim (endurance limit measured in time).
The systematic review (Annane et al. 2009) identified eight randomised control trials investigating the efficacy of nocturnal NIV in relieving hypoventilation related symptoms in patients with neuromuscular and chest wall disorders. Neuromuscular in this review included people with ALS. The primary outcome measure was reversal of daytime hypoventilation symptoms including diurnal hypersomnia and headaches with few studies reporting lung function measurements. The finding of the review was that although the evidence supporting mechanical ventilation was weak, it was consistent in suggesting benefit in the short term.
Seven studies investigated the effect of NIV on lung function in people with ALS (n=391). Four studies (n=282) demonstrated a slower decline in FVC in people who could tolerate NIV (Bourke et al. 2003; Carratu et al. 2009; Kleopa et al. 1999; Lo Coco et al. 2006). As the main focus of these studies was survival, NIV intervention was non-standardised i.e. it was

individualised to the patient, in terms of mode and length of time of intervention. The evidence is weakened by the fact that Kleopa et al (1999) and Carratu et al (2009) are retrospective studies.

Inconclusive evidence exists in relation to other measures of lung function. Aboussouan et al (2001) found no change in FVC, FEV_1, MIP or MEP; Butz et al (2003) identified increased oxygenation (S_aO_2 and P_aO_2) and Lechtzin et al (2006) showed increased lung compliance following NIV. This increase in compliance would then result in a decrease in load and potentially improve the balance between load and capacity, despite no change in MIP. Two studies, including 29 subjects with a range of neurodegenerative conditions, identified increased respiratory muscle endurance (Goldstein et al. 1991) and improved oxygenation (Nauffal et al. 2002) following NIV intervention.

The key findings from these studies are that NIV may have an influence on lung function in people with ALS/MND and recommendations have been made for its use within these groups as an intervention to improve quality of life and survival as well as alleviating breathlessness. It would be interesting to explore, from a clinical perspective, why NIV has not been investigated in other neurodegenerative conditions such as MS and PD and whether it may be effective in improving lung function in these groups.

Table 43 Studies related to non-invasive ventilation

a) Systematic review				
Author	**Title**	**Sources**	**Method**	**Results**
Annane et al 2009	Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest disorders	MEDLINE (January 1966-June 2006) EMBASE (January 1980–June 2006) Cochrane neuromuscular disease group trials register	Inclusion criteria: Randomised controlled trial, with or without blinding; people with neuromuscular and chest wall disorder related stable chronic hypoventilation; all ages; all severity; any type and mode of nocturnal mechanical ventilation. Exclusion criteria: People with COPD Independently reviewed by 2 reviewers.	15 studies found, 8 met inclusion criteria. Conclusion: Evidence regarding nocturnal mechanical ventilation is weak, but consistent, suggesting short term alleviation of hypoventilation.

b) Individual studies			
Study	**Population**	**Intervention and comparison**	**Key significant findings**
Aboussouan et al 2001	60 ALS	Single group, repeated measures over time of FEV_1, FVC, MIP, MEP during: NIV: volume controlled or BiPAP with pressures for patient comfort, for as long as tolerated during night and as necessary daytime.	Rate of decline in FEV_1, FVC unchanged with NIV. No change in MIP, MEP.
Bourke et al 2003	17 ALS	Single group, repeated measures over time of VC, MIP, MEP, SNIP during: NIV, pressures adjusted according to blood gas analysis and patient comfort	Rate of decline in VC slower post treatment p=0.039
Butz et al 2003	30 ALS	Single group, repeated measures over time of VC, $PaCO_2$, PaO_2, SaO_2 during NIV: pressure cycled; pressures 8-22 millibars dependent upon arterial blood gases, oxygen saturation and relief of symptoms	PaO_2 improved at 4 months p=0.01 SaO_2 improved up to 7 months p=0.027

Study	Population	Intervention and comparison	Key significant findings
Carratu et al 2009	72 ALS	Retrospective study, comparing FVC in: A FVC>75%predicted, no NIPPV B FVC<75% predicted and tolerant of NIPPV C FVC<75% predicted and refused or intolerant of NIPPV NIPPV: Volume controlled or BiPAP; pressures – 8cmH_2O BiPAP, 3cmH_2O EPAP; volume/pressure dependent upon chest rise, leaks and comfort; used nightly as tolerated and as necessary daytime.	FVC decline slower in B than C p<0.0001
Goldstein et al 1991	6 including 2 neurodegenerative conditions	Single group, repeated measures over time of FEV_1, FVC, FEV_1/FVC, MIP, MEP, MVV, Tlim during: NIV: volume cycled , as tolerated by participant	Tlim ↑ at 3 months post intervention p<0.05
Kleopa et al 1999	122 ALS	Retrospective study, comparing FVC % predicted in, A those who tolerated BiPAP for >4 hours B those that tolerated <4 hours C those who refused.	A slower decline of FVC %predicted than B, p=0.02 and C, p<0.001
Lechtzin et al 2006	19 ALS, 4 healthy control	2 groups , compared MIP, MEP, lung compliance A ALS with BiPAP B Healthy control with BIPAP BiPAP for 5 minutes, dependent upon lung compliance	A ↑Lung compliance with BiPAP B no change

Study	Population	Intervention and comparison	Key significant findings
LoCoco et al 2006	71 ALS	Single group, repeated measures over time comparing FVC % predicted, FVC variation over time BiPAP: pressures adjusted to patient comfort, leaks and efficiency of ventilation; for as long as tolerated nightly and as necessary daytime	Decline of FVC slower in those who could tolerate NIV p=0.002
Nauffal et al 2002	62 including 27 neurodegenerative conditions	Single group, repeated measures over time comparing FEV_1 %predicted, FVC %predicted, TLC, SaO_2, MIP, PaO_2, PaO_2 during: BiPAP nightly; pressures dependent on arterial blood gases.	For people with neurodegenerative condtions:SaO_2, ↑ after 3 months p<0.05, FEV_1, FVC ↓ after 12 months

Key to Table 43

COPD	Chronic obstructive pulmonary disease
ALS	Amyotrophic lateral sclerosis
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
FEV_1/FVC	Forced expiratory volume in 1 second/ Forced vital capacity ratio
VC	vital capacity
MIP	Maximal inspiratory pressure
MEP	Maximal expiratory pressure
SNIP	Sniff nasal inspiratory pressure
NIPPV	Non-invasive positive pressure ventilation
NIV	Non-invasive ventilation
BiPAP	bilevel positive airway pressure
EPAP	Expiratory positive airway pressure
P_aO_2	Partial pressure of oxygen in arterial blood
PaCO2	Partial pressure of carbon dioxide in blood
S_aO_2	Saturation of oxygen

7.5.2 Respiratory muscle training

Ten studies, including four randomised control studies, see Table 44, were found that assessed the effect of respiratory muscle training in people with neurodegenerative conditions. Outcome measures used in the studies include maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP) and 12 second maximal voluntary ventilation (12MVV).

Five studies investigated inspiratory muscle training and identified significant increases in MIP post intervention: two randomised control studies in 61 people with MS (Fry et al. 2007; Klefbeck and Nedjad 2003); an experimental study in MS with 46 participants (Pfalzer and Fry 2011) and one study including 20 people with PD (Inzelberg et al. 2005). The trial by Cheah et al (2009) only demonstrated trends of increased inspiratory pressure measured by MIP and sniff nasal inspiratory pressure (SNIP) when compared to sham inspiratory muscle training in 19 people with ALS. The studies lasted between 10 and 12 weeks with training ranging from daily to every other day. Although Fry et al (2007) and Pfalzer and Fry (2011) did not see a change in MVV, Inzelberg et al (2005) did see a significant increase in inspiratory muscle endurance as measured by the peak pressure obtained on breathing against progressive loads to fatigue.

The effect of expiratory muscle training (EMT) on maximal expiratory pressure (MEP) is less clear than the effect of inspiratory muscle training (IMT) on MIP. Two randomised control trials demonstrated significant increases in MEP in 48 people with MS compared to breathing exercises (Gosselink et al. 2000) and control group (Smeltzer et al. 1996). Chiara et al (2006) also found significant increases in MEP in 17 people with MS after 8 weeks training; this was not significantly different to the group of healthy control subjects who carried out the same training. A shorter study by Pitts et al (2009) of 4 weeks EMT in people with PD showed a significant increase in MEP, but no difference in peak cough flow. The length of training: daily for 3 months (Gosselink et al. 2000; Smeltzer et al. 1996); daily for 8 weeks (Chiara et al. 2006); 5 days/week for 4 weeks (Pitts et al. 2009) and different stages of disease: mild (Smeltzer et al. 1996) mild/moderate (Chiara et al. 2006; Pitts et al. 2009) and severe (Gosselink et al. 2000) may explain the different results.

In a pilot study by Olgiati et al (1989), 8 people with MS were assigned either IMT or EMT, dependent upon whether the subjects MIP or MEP was <70% predicted. Although training was only for 4 weeks, significant increases were observed in MIP, MEP and MVV for the whole group.

There is some evidence that specific inspiratory and expiratory muscle training does increase MIP and MEP respectively, and also respiratory muscle endurance in people with neurodegenerative conditions. The majority of studies were carried out on people with MS and therefore results may not be inferred to people with other neurodegenerative conditions. Although a number of the studies were randomised controlled trials, the interventions and outcomes used differed, making overall conclusions difficult to make.
A similar review was undertaken after this work had been completed and cites Jones et al. (2012b), used a similar search strategy, reviewed the same studies and came to the same conclusions (Reyes et al. 2013).

Table 44 Studies related to respiratory muscle training

Study	Population	Intervention and comparison	Key significant findings
Cheah et al 2009	19 ALS	2 groups, comparison of VC, FVC, MIP, MEP, SNIP A IMT group B Sham group, no resistance IMT 10 minutes, 3 times daily, 12 weeks. Threshold device, resistance increased weekly from 15 to 60% SNIP, then sustained at 60% SNIP.	Adherence IMT 82%, Sham 85% Non- significant increase in FVC, MIP, SNIP in both groups
Chiara et al 2006	17 MS, 14 healthy control	2 groups, repeated measures pre, post and 4 weeks after intervention, comparing FEV_1, FVC, PEFR, MEP, PCF A MS & EMT B Healthy control & EMT EMT 4 sets of 6 repetitions, 5 days a week, 8 weeks. Threshold device, resistance increased weekly from 40 to 80% MEP then sustained at 80% MEP	Adherence >90% A & B ↑MEP, PEFR after 8 weeks $p<0.01$ and sustained through no training no difference between groups
Fry et al 2007	46 MS	2 groups, comparison of FEV_1, FVC, VC, MIP, MEP, MVV A Home IMT group B Control group no intervention Threshold device, IMT 3x15 reps, daily for 10 weeks. Resistance altered according to baseline MIP, perceived exertion and symptoms	Adherence 81% A ↑MIP $p=0.001$; FVC $p=0.04$; FEV_1 $p=0.01$; FEV_1/FVC predicted $p=0.016$; VC $p=0.009$ compared to B

Study	Population	Intervention and comparison	Key significant findings
Gosselink et al 2000	28 MS	2 groups, comparison of FVC, MIP, MEP, cough efficacy A EMT B Breathing exercises EMT 3 sets of 15 repetitions, twice daily for 3 months. Threshold device, resistance was 60% MEP. Breathing exercises to enhance maximal inspirations	A ↑Cough efficacy compared to B $p<0.05$ A ↑MIP from baseline but not different to B
Inzelberg et al 2005	20 PD	2 groups, comparison of FEV_1, FVC, MIP, inspiratory muscle endurance (PmPeak) A IMT B Sham Threshold device, IMT: 30mins, 6 days/week, 12 weeks. Resistance increased from 15 to 60% MIP and sustained at 60% MIP. Control frequency as IMT. Resistance 7cmH_2O	A ↑MIP, PmPeak $p=0.05$
Klefbeck and Nedjad 2003	15 MS	2 groups, comparison of FEV_1, FVC, VC, PEFR, MIP, MEP A IMT B Control Threshold device, IMT: 3 sets of 10 repetitions, twice every other day, 10 weeks. Resistance 40-60% MIP. Control deep breathing exercises as part of physiotherapy treatment.	A ↑MIP $p=0.008$ and MEP $p=0.02$ from baseline A ↑MIP significant compared to B $p = 0.01$

Study	Population	Intervention and comparison	Key significant findings
Olgiati et al 1988	8 MS	Single group, comparison of VC, RV, TLC, MIP, MEP, MVV pre and post intervention. IMT /EMT dependent upon % MIP/MEP Device type not stated, training 6-10 minutes, twice/day, 5 days/ week for 4 ±1 week. Resistance dependent upon %MIP/MEP and progressively increased.	↑MIP $p<0.02$, MEP $p<0.05$, MVV $p<0.05$
Pfalzer and Fry 2011	46 MS	2 groups, comparison of FEV_1, FVC, MIP, MEP, MVV A IMT B Control Threshold device, 3 x 15 reps, daily for 10 weeks,	Adherence 81% A ↑MIP compared to B, $p=0.003$
Pitts et al 2009	10 PD	Single group, comparison of MEP, PCF pre and post EMT Threshold device, training 5 sets of 5 breaths, once/day, 5 days week for 4 weeks. Resistance 75% of MEP	↑MEP $p=0.005$, PCF $p=0.01$
Smeltzer et al 1996	20 MS	2 groups, repeated measures over time comparing MIP, MEP A EMT B Sham, IMT at low load Threshold device, EMT 3 x 15 repetitions, twice daily for 3 months. Resistance based on MEP	A ↑MEP compared to B

Key to Table 44

PD	Parkinson's disease
ALS	Amyotrophic lateral sclerosis
MS	Multiple sclerosis
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
VC	Vital capacity
TLC	Total lung capacity
PEFR	Peak expiratory flow rate
PCF	Peak cough flow
MIP	Maximal inspiratory pressure
MEP	Maximal expiratory pressure
SNIP	Sniff nasal inspiratory pressure
MVV	Maximal voluntary ventilation
IMT	Inspiratory muscle training
EMT	Expiratory muscle training

7.6 Summary of evidence on physiotherapy management of respiratory problems in people with neurodegenerative conditions

The review selected 37 studies related to physiotherapy based interventions for respiratory function. Populations were defined clearly in all studies; only two studies carried out power calculations. In those studies (n=6) that required allocation to groups, this was defined. Random allocation was defined in the seven randomised controlled trials. Reproducibility of interventions was variable (14/35 not reproducible), reasons included retrospective studies and inadequate information. All outcome measures were defined, reliable and valid, but different outcome measures were used in comparable studies. Generalizability of the findings was low for the majority of studies due to lack of power and non-reproducible interventions. The evidence selected was weak due to lack of power and lack of reproducibility of interventions, as highlighted in Appendix 6.

This systematic review was limited by the number and quality of studies and consequently a meta–analysis was not feasible. The studies had heterogeneous populations, were under powered, often non-randomised and of insufficient number to provide guidelines for management of the different stages of progressive conditions. Interventions and outcome measures were not standardised between studies. The process of review was limited by having one reviewer rather than two, thus introducing potential bias to the review. This was minimised by using the PICO structure (The Joanna Briggs Institute. 2008) for searching and the CASP appraisal tool (Critical Appraisal Skills Programme. 2007) for evaluation of studies.

The management of retained secretions included increasing lung volume, mobilising secretions and maximising cough efficacy. For people with neurodegenerative conditions and susceptibility to type 1 respiratory failure, assisted cough strategies may improve cough effectiveness. There is no evidence to support the use of high frequency chest wall oscillation to mobilise secretions and inconclusive evidence regarding methods to increase lung volume. This inconclusive evidence implies that management of increased load in people with neurodegenerative conditions requires further investigation. Exercise as an intervention should be explored further based on the findings of Mostert and Kasserling (2002) and Rasova et al. (2006).

Decreased capacity in people with neurodegenerative conditions is predominantly managed by reducing the work of breathing by non-invasive ventilation, which shows weak positive

effects. There is some evidence that respiratory muscle strength may be increased through specific training programmes.

Inspiratory muscle weakness is suggested as an important determinant in respiratory dysfunction in people with neurodegenerative conditions (Benditt and Boitano 2013; Buyse 2006; Polkey et al. 1998) and was identified in the observation study to be a key element in respiratory dysfunction in people with HD. There is some evidence from the preceding review that inspiratory muscle training (IMT) may increase strength and endurance in people with neurodegenerative conditions and therefore it was decided to explore IMT in more depth as a potential intervention for people with HD. Training of respiratory muscles in people with and without pathological conditions has been researched for the last 40 years and further exploration of physiological mechanisms and benefit was necessary to determine if IMT was a feasible intervention for people with HD. The specific question to be answered in the second review was 'what is the effect of inspiratory muscle training in untrained and trained healthy subjects and in people with respiratory conditions in relation to the World Health Organisation' International Classification of Functioning, Disability and Health'.

7.7 Search strategy: Inspiratory muscle training

The search was limited to English language articles found using the following databases: Medline, EMBASE, AMED and CINAHL, from inception to September 2013. The search was carried out using an historical approach alongside a structured PICO approach. In the historical approach, specific studies were sought that developed the theory underpinning inspiratory muscle training based on the original Leith and Bradley (Leith and Bradley 1976) study and related to the principles of resistance training.

The CASP approach was used to evaluate efficacy of inspiratory muscle training in healthy trained and untrained subjects as well as people with pulmonary health conditions. The review was written within the context of the World Health Organisation' International Classification of Functioning, Disability and Health (World Health Organisation. 2009) and therefore outcome measures were related to body function and structure and activity.

Populations keywords were: 'healthy', 'trained', 'untrained', 'athletes', 'chronic obstructive pulmonary disease', 'cystic fibrosis', 'asthma'.

Intervention keywords were: 'inspiratory muscle training', 'respiratory muscle training'.

Outcome keywords were: 'resp*', 'pulmonary', 'lung', 'performance'.

Studies were excluded if: the population was <18, inspiratory muscle training was combined with other interventions, subjects were ventilated, case studies, abstracts.

7.8 Inspiratory Muscle Training

7.8.1 Skeletal muscle strength training

The current principles of strengthening skeletal muscle date back to 1945 (DeLorme 1945), presumably due to an increase in injured soldiers returning from war. Captain Thomas DeLorme of the United States Medical Corps transformed exercise training by introducing progressive resistive exercises which utilised the principles of overload and specificity to strengthening muscles. Progressive overload is the gradual increase of stress placed on the body in order for improvement to be made (Kraemer and Ratamess 2004). DeLorme (1945) achieved overload by assessing the one repetition maximum strength (1-RM) and the 10 repetition maximum strength (10-RM) and using these values to set the initial and increasing load. Overload can also be introduced by increasing the number of repetitions or speed of repetition; changing the rest period; increasing the volume and by any combination of these variables. Shortening the rest period may improve local muscle endurance, whilst lengthening it may improve strength and power (Kraemer and Ratamess 2004).

Specificity relates to the type of exercise and the consequent functional changes, as all training adaptations are specific to the stimulus applied. Adaptations are specific to the individual muscles and muscle groups involved; the range of motion in which the training was performed; the speed of movement; the energy systems involved and the intensity and volume of training (Kraemer and Ratamess 2004). The original exercise dose prescribed by DeLorme (1945) was 70-100 repetitions, once a day, five days per week. The exact numbers were not rationalised, but it was felt that a single session per day would not be tiresome for the participant and that they should rest on the days when not doing exercise. There was no physiological reason given for the rest, possibly the days rested were weekends. These principles of progression using overload and specificity are still core to the setting of exercise programmes in healthy adults (Kraemer et al. 2002). For novice healthy people i.e. those who have not trained previously, the American College of Sports Medicine (ACSM) recommend a load of 60-70% of 1RM, 1-3 sets of 8-12 repetitions with 2-3 minutes rest between sets, 2-3 times per week. For intermediate and advanced people the load, velocity and frequency is increased (Kraemer et al. 2002). Guidelines for prescription of exercise for people with pathology are provided by the ACSM (American College of Sports Medicine. 2010)

Changes in skeletal muscle strength may be due to factors other than muscle hypertrophy and include volition, motor neuron activity and co-ordination of limb stabilising muscles (Rutherford and Jones 1986). Neuronal adaptions appear to occur in the first two weeks of

training and include increased motor-unit recruitment and firing frequency, whilst hypertrophy proceeds linearly throughout training. Hypertrophy is greater in type 2 muscle fibres and is thought to be due to individual muscle fibre growth and proliferation (Folland and Williams 2007).

The third principle of strength training, alongside overload and specificity is reversibility. Strength that is lost through inactivity can be regained during a similar time period of resistance training (Campbell et al. 2013) and gains during training can be subsequently lost when training ceases. The extent of the loss is dependent on age, the length of cessation of exercise and training status (Bosquet et al. 2013).

7.8.2 Principles of skeletal muscle training applied to respiratory muscles

When Leith and Bradley (1976) first investigated inspiratory muscle training (IMT) in human subjects, their primary question was whether respiratory muscles like other skeletal muscles could be specifically trained to increase strength and endurance. An increase in strength and endurance of respiratory muscles could then lead to improved performance in two distinct categories of people. One category is those who have 'normal' respiratory systems and needed to exercise against added ventilatory loads e.g. divers and firemen, with the second category being those with respiratory diseases where ventilation limits exercise. The Leith and Bradley study found, similar to the original DeLorme findings, that specific strength training improved respiratory muscle strength and specific endurance training improved respiratory muscle endurance. Although there are some flaws to the study, small numbers (n=12, 4 in each group) and non-naive subjects, this study was the basis for the development of research on inspiratory muscle training and its use within people with 'normal' respiratory systems and those with conditions that altered the load on the respiratory system.

Tzelepis et al (1994a) further explored Leith and Bradley's concept of specificity of training by relating flow during inspiration to the velocity of muscle shortening and relating the pressure generated during inspiratory with force generation. Drawing on evidence regarding the specificity of force-velocity training from other skeletal muscle research, this study investigated single gasps as high velocity training and maximal static inspiratory efforts as high force training. A third group performed intermediate velocity and force manoeuvres, whilst a fourth group acted as a control. Like Leith and Bradley (1976), Tzelepis et al (1994a) confirmed that respiratory muscles did respond to specific training programmes, with high velocity training improving flow, high force training improving strength and combined training increasing flow and strength.

Tzelepis et al (1994b) then went on to look at specificity of lung volume on training, in healthy participants, with the reasoning that the greatest improvement in strength will occur only at the length at which the muscle is trained. Following 6 weeks isometric training at residual volume, relaxed end expiratory volume and relaxed end expiratory volume plus half of the inspiratory capacity, the greatest strength improvements were found at the specific volume at which the training took place. The greatest increase in strength was found at lower lung volumes, i.e. when the diaphragm is at optimal length (De Troyer and Wilson 2009). Tzelepis et al (1994b) postulated that the specific volume related strength increase may be due to neuromuscular adaptation as well as increase in muscle cross sectional area.
Romer and McConnell (2003) developed these ideas further, again in healthy participants, by evaluating pressure-flow specificity of inspiratory muscle training and the effects of de-training and reduced frequency of training on these adaptations. Analysis of pressure-flow-power relationships of inspiratory muscle function demonstrated that after 9 weeks of training, high pressure training produced the largest improvements in pressure (strength); high flow training produced the largest improvements in flow (velocity) and intermediate training resulted in a more uniform increase in pressure and flow. Intermediate training produced the greater improvement in power of the inspiratory muscles. When the frequency of training was reduced from six days per week to two days per week, the gains in respiratory function were maintained whereas no training resulted in small but significant reductions in respiratory muscle function. As the period of training in this study was longer than Tzelepis et al (1994b), Romer and McConnell (2003) attribute the early changes (first 5-6 weeks) to neural adaptations or skill acquisition as described by Moritani (1993) whereas later in the training period muscle hypertrophy and transformation of muscle fibre may have produced the strength changes. Diaphragm hypertrophy following IMT has been confirmed on ultrasound by both Enright (2006b) and Downey (2007). Table 45 gives further detail on the above studies.

Table 45 Studies related to background of respiratory muscle training

Author	Participants	Intervention and comparison	Outcome
Leith and Bradley 1976	12 healthy	A Control group – unknown protocol B static inspiratory and expiratory manoeuvres at 20% intervals over VC range 30mins/day C ventilated to exhaustion 3-5 times, lasted 45-60mins 5 days/week, 5 weeks	B ↑MIP, MEP, VC $p<0.05$ C ↑MVV $p<0.05$
Romer and McConnell 2003	24 healthy	A Low flow, high pressure 10 sets of 3 maximal inspiratory efforts from RV with static 2-3 second hold, minimal recovery between sets B High flow, low pressure 30 maximal inspiratory efforts, no resistance C Intermediate flow and pressure 30 maximal inspiratory efforts at 50%MIP D no training 6 days/week, for 9 weeks Then randomly assigned to 2 days/week OR no IMT for 9 weeks	Adherence A 91%, B 88%, C 89%, M 90% No change in FVC, FEV_1, PEFR in any groups or between groups A ↑Maximum pressure at zero flow (P_0), no change maximum pressure at maximal flow ($\dot{V}_{max}$) B ↑ $\dot{V}_{max}$, no change P_0 C ↑P_0, ↑$\dot{V}_{max}$ All $p<0.05$ D no change P_0 or V_{max} No IMT detraining: ↓P_0 and V_{max} Maintenance IMT: no change P_0, P_{max}
Tzelepis et al 1994a	19 healthy	A 30 maximal static inspiratory efforts at end expiratory relaxation volume B 30 x 3 maximal inspiratory efforts, no resistance C 30 maximal inspiratory efforts with 7mm resistor D control – unknown protocol Rests between sets not defined 5 days/week for 6 weeks	A ↑maximal oesophageal pressure B ↑ flow C ↑ maximal oesophageal pressure and flow All $p<0.05$ D no change in flow or maximal oesophageal pressure

Author	Participants	Intervention and comparison	Outcome
Tzelepis et al 1994b	27 healthy	A isometric strength training at RV B isometric strength training at end expiratory relaxation volume C isometric training at end expiratory relaxation volume + ½ IC D control no training 30 max manoeuvres, rests between sets not defined, 5days/week for 6 weeks	A, B, C ↑ MIP $p<0.05$ Greatest change within groups was at the specific training volume. Broadest range of increases was in the group training at lowest lung volume No difference in VC or TLC within or between groups

Key to Table 45

FEV_1	Forced expiratory volume in 1 second	MEP	Maximal expiratory pressure
FVC	Forced vital capacity	MVV	Maximal voluntary ventilation
VC	Vital capacity	RV	Residual volume
PEFR	Peak expiratory flow rate	IMT	Inspiratory muscle training
MIP	Maximal inspiratory pressure	IC	Inspiratory capacity

7.9 Methods of inspiratory muscle training

Following initial positive evidence that IMT could strengthen and increase endurance of respiratory muscles in healthy volunteers, further research was carried out on trained athletes and people with conditions resulting in increased load on the respiratory system. These studies used a number of methods to achieve training including voluntary isocapnic hyperpnoea, flow resistive loading and pressure threshold loading. Voluntary isocapnic hyperpnoea does not provide external resistance to breathing, but requires individuals to breath at high respiratory rates for up to 30 minutes. Appropriate CO_2 levels are maintained by supplemental O_2 (Sheel 2002). This can be uncomfortable, particularly for people with respiratory limitations and therefore tends to be confined to laboratory studies (McConnell and Romer 2004).

Flow resistive loading involves individuals breathing through a variable diameter of mouthpiece, with a smaller diameter producing greater resistive load. Issues with this method include the fact that individuals can alter their flow by altering breathing pattern, which negates the resistive load applied (McConnell and Romer 2004). Chatham et al (1996) further developed the idea of flow resistive training through the test of incremental respiratory endurance (TIRE). This method requires individuals to perform sustained maximal inspiratory efforts through a 2mm diameter orifice at 80% of their maximal effort. Training involves six breathes at 80% maximal effort, repeated up to 6 times with decreasing time periods between each set of six breaths. The decreasing rest periods are recommended for endurance training, compared to longer rest periods recommended for strength training (Kraemer et al. 2002). The TIRE method requires an electronic manometer and computer with specific software for the training programme.

Pressure threshold training requires individuals to overcome a negative pressure provided by the device in order to initiate inspiration. Devices used in studies include a weighted plunger, spring loaded poppet valve and solenoid valve (McConnell and Romer 2004). Although theoretically the initial load to be overcome would only have effect at the particular volume at which the inspiration occurs based on the work by Tzelepis (1994b), when moderate pressure loads and moderate flow rates are used improvements have been noted at both extremes of the force-velocity relationship (Romer and McConnell 2003). A relatively new technological development is the POWERbreathe® Medic threshold trainer which provides a variable resistance throughout inspiration from residual volume to total lung capacity to provide a load through the full range of muscle work.

7.10 Efficacy of inspiratory muscle training

The physiological and clinical basis of respiratory muscle training remains controversial. Proponents cite systematic reviews and meta-analyses that provide statistical evidence for its use, based upon improvements in exercise limitation (Ambrosino 2011; McConnell 2012); opponents cite inappropriate methodologies and question whether respiratory muscles can be strengthened in people with COPD as the diaphragm is at a mechanical disadvantage due to hyperinflation (Patel et al. 2012) as well as the learning effect of intervention manoeuvre being similar to the outcome measure (Polkey and Moxham 2004). The evidence on respiratory muscle training spans a wide range of subject groups e.g. healthy trained and untrained and people with health conditions and different outcome measures e.g. respiratory muscle strength and endurance, exercise tolerance and performance. Polkey et al (2011) recommend that measures of body structure and function i.e. respiratory muscle strength and endurance, should not be the primary outcome measure of studies, as preference should be given to measures of activity. This, in part, is based on the view that patients do not present to their doctors complaining of weak respiratory muscles, but rather limitations in activity and participation (Polkey et al. 2011). In order to cover the range of studies, this section will use the framework of the World Health Organisation's International Classification of Functioning, Disability and Health (World Health Organisation. 2009), to review the evidence regarding respiratory muscle training on body function and structure, activities and participation in relation to those with 'normal' respiratory systems and those with health conditions that increase the load on the respiratory system. Description of studies is provided in Tables 46-49, critical appraisal in Appendix 6.

7.10.1 Body Function and structure

IMT, with the exception of TIRE, does not alter pulmonary function in healthy untrained subjects (Edwards et al. 2008; Kellerman et al. 2000; Suzuki et al. 1993); healthy trained subjects (Inbar et al. 2000; Williams et al. 2002); people with cystic fibrosis (Houston et al. 2008) and people with asthma (Ram et al. 2009). In two recent systematic reviews on people with chronic obstructive pulmonary disease, pulmonary function was not reviewed (Geddes et al. 2008; Gosselink et al. 2011). Three studies using TIRE do show increases in vital capacity in healthy untrained (Enright et al. 2006b; Enright and Unnithan 2011) and healthy trained subjects (Mickleborough et al. 2010).

Maximal inspiratory muscle strength after interventions using both pressure threshold devices and TIRE is increased in healthy untrained subjects (Downey et al. 2007; Edwards et al.

2008; Enright et al. 2006b; Enright and Unnithan 2011; Witt et al. 2007) and in trained cyclists (Romer et al. 2002a); endurance (Inbar et al. 2000) and recreational runners (Kwok and Jones 2009; Mickleborough et al. 2010); rowers (Volianitis et al. 2001) and wheelchair athletes (Goosey-Tolfrey et al. 2010). Sustained maximal inspiratory pressure was also increased in healthy subjects (Enright et al. 2006b; Enright and Unnithan 2011). This is supported by evidence that diaphragmatic thickening occurs as a result of IMT (Downey et al. 2007; Enright et al. 2006b) confirming that changes in strength are due not only to neural adaptations but changes in the muscle fibres. The evidence in people with conditions that increase load on the respiratory system is less clear. Evidence from systematic reviews on IMT in people with COPD agrees that IMT increases inspiratory muscle strength (Geddes et al. 2008; Gosselink et al. 2011) yet the evidence in people with CF (Reid et al. 2008) and asthma (Ram et al. 2009) is weak. Strength gains in people with COPD are supported by changes in the proportion of type I fibres and size of type II fibres (Ramirez-Sarmiento et al. 2002).

7.10.2 Activity and Participation

Dyspnoea is a sensation that restricts activity and is derived from physiological, psychological, sociological and environmental factors (Parshall et al 2012). The physiological element relates to the balance between load and capacity and therefore IMT aims to increase capacity to offset an increase in load and consequently reduce the sensation of dyspnoea. Evidence for a reduction of dyspnoea in healthy untrained subjects is weak (Downey et al. 2007), but is very strong in people with COPD and accompanies an increase in exercise capacity and quality of life (Geddes et al. 2008; Gosselink et al. 2011).

Evidence related to exercise capacity in healthy subjects is dependent upon level of fitness, interventions and activities measured. In untrained healthy subjects, Chatham et al (1999) and Edwards et al (2008) demonstrated increased predicted and actual $\dot{V}O_{2max}$ values respectively, whilst Downey et al (2007) demonstrated improved ventilation and gaseous exchange in exercise in hypoxic conditions and Enright and Unnithan al (2011) demonstrated increased work capacity.

Two systematic reviews and meta-analyses on the effects of inspiratory muscle training on performance in healthy individuals (Illi et al. 2012) and athletes (HajGhanbari et al. 2013) concluded that endurance performance improved independently of the type of training (strength or endurance) or the type of sport. Additionally, Illi et al. (2012) found that less fit individuals benefited more than highly trained athletes. This range of fitness in healthy

subjects may be comparable to range of respiratory muscle strength in people with health conditions and as such, larger differences may be seen in those with weaker muscles (Gosselink et al. 2011).

7.10.3 Relationship between 'body function and structure' and 'activity and participation'

The mechanism underlying the relationship between respiratory muscle strength and exercise capacity is thought to relate to blood flow alterations when diaphragmatic fatigue occurs. Romer and Polkey (2008) suggest that this relationship may be dependent on cardiorespiratory interactions and describe a reflex decrease blood flow to peripheral muscles when respiratory fatigue occurs. The reflex comprises an increase in metabolites produced by the fatiguing diaphragm, which stimulates sympathetic efferent discharge, causing vasoconstriction of the locomotor muscles. The consequence of this is locomotor fatigue which can lead to an increase in perception of effort and limitation of high intensity performance (Dempsey et al. 2006). It is thought that this reflex results in increased blood flow to the diaphragm in preference to the locomotor muscles, but the exact balance is still unknown (Dempsey 2012). Respiratory muscle fatigue could occur when there is an imbalance between load and capacity which would arise in healthy subjects exercising at high intensities >80% $\dot{V}O_{2max}$ (Dempsey et al. 2006), in people with respiratory conditions exercising at relatively lower intensities, and when the load on the respiratory system is suddenly increased. It is thought that inspiratory muscle training attenuates this reflex by reducing the energy requirements of the respiratory muscles thereby enhancing performance (Turner et al. 2012),

7.11 Summary of inspiratory muscle training review

Respiratory muscles may be strengthened by progressive exercise training and are governed by the same principles of overload, specificity and reversibility which exist in peripheral skeletal muscles (Romer and McConnell 2003). Evidence is not consistent across untrained, trained, people with respiratory problems and people with neurodegenerative conditions which is likely to be due to inconsistent methods and outcome measures between studies. Interventions differ in key programme variables such as muscle action used; intensity, volume and frequency of exercises and rest periods between sets. Measures of respiratory muscle strength tend to be similar i.e. MIP but measurement of respiratory muscle endurance is not consistent. Measures of functional ability related to the specific participant group

(untrained/trained/with respiratory or neurodegenerative conditions). The strongest evidence for people with respiratory conditions is for people with COPD based on a systematic review (Gosselink et al. 2011) with little evidence for those with neurodegenerative conditions (Jones et al. 2012b; Reyes et al. 2013).

One of the main arguments against inspiratory muscle training in people with COPD is that the respiratory muscles may not be weak in a physiological sense, but are biomechanically weak due to hyperinflation (Polkey and Moxham 2004), but this argument may not be true for people with neurodegenerative conditions. Decreased capacity i.e. decreased respiratory muscle strength is the primary cause of respiratory failure in this group (Buyse 2006) and therefore respiratory muscle training appears to be a potential management option. Strength training involves muscular and neural adaptations (Folland and Williams 2007) and therefore integrity of these systems must exist for improvements to occur. However, neural plasticity may occur throughout the respiratory neuromuscular pathway from respiratory drive to the neuromuscular junction and respiratory muscles (Johnson and Mitchell 2013) therefore strength training may be effective. Increased neural drive has been noted following lower limb resistance training in people with MS (Dalgas et al. 2013), but this has not been investigated in respiratory muscle training.

The measurement of effectiveness of respiratory muscle training is dependent upon the reasons for increasing respiratory muscle strength. Respiratory muscle strength is thought to be the beginning of a causal chain which leads to reduced pulmonary function and death (Buchman et al. 2008a) which in itself is a strong reason why respiratory muscle training should be investigated, with respiratory muscle strength as an outcome measure. The complexity of relationships between respiratory muscle strength, peripheral muscle strength, pulmonary function and mortality (Buchman et al. 2008a) and between FEV_1, physical activity and mortality (Jakes et al. 2002) provides a number of outcome measures that may be used when assessing the impact of respiratory muscle training. In relation to the proposed framework of respiratory failure in people with HD the primary outcome measure should be inspiratory muscle strength in order to investigate physiological changes in body structure and function and a functional measure as recommended by Polkey et al. (2011).

Table 46 Studies related to untrained healthy participants

Author	Participants	Intervention	Outcome
Chatham et al. 1999	22 healthy	A TIRE training: up to 36 SMIP manoeuvres at 80%MIP, 6 sets of 6 with decreasing rests between sets i.e. 45, 30, 15, 10 and 5 seconds rest, until unable to follow training template. 3days per week for 10 weeks B Control training as above 3 days/week in week 1 and 10. No training weeks 2-9. Flow resistance device	A ↑ MIP $p<0.002$, SMIP $p<0.0001$, predicted $\dot{V}O_{2max}$ $p<0.001$, no change in dyspnoea in shuttle run B no change
Downey et al. 2007	15 healthy	A threshold device, 40 maximal inspirations at 50% MIP B threshold device, 40 maximal inspirations at 15% MIP Rest period not defined 2 per day, 5 days/week for 4 weeks	A ↑MIP, diaphragm thickness, ↓ respiratory muscle fatigue in hypoxia and normoxia ↔$\dot{V}O_2$ in normoxia ↓$\dot{V}O_2$, Cardiac output, VE, lung diffusing capacity, RPE and dyspnoea in hypoxic exercise All $p<0.05$ B no change Significant difference between A and B, $p<0.05$
Edwards et al. 2008	16 healthy males	A 30 breaths at maximal resistance possible B 30 breaths 15%MIP Threshold device, no rest period defined 30 breaths, 1/day, 7days/week for 4 weeks	A, B no change in lung volume A, B, ↑ MIP $p<0.01$, $\dot{V}O_{2max}$ $p<0.05$, ventilatory threshold $p<0.05$ A ↓RPE $p<0.05$, 5K run time compared to B $p<0.05$ A↑ MIP more than B $p<0.05$ No difference in maximal aerobic power, ventilatory threshold between A and B

Author	Participants	Intervention	Outcome
Enright & Unnithan 2006	20 healthy	A 1 week habituation, TIRE as per Chatham 1999 3days/week for 8 weeks B no training	100% adherence A ↑MIP, SMIP $p<0.01$ ↑VC, TLC ↑diaphragm thickness, exercise capacity $p<0.05$ Significant differences between A and B $p<0.05$
Enright et al. 2011	40 healthy	A TIRE protocol 80% SMIP B TIRE protocol 60% SMIP C TIRE protocol 40% SMIP D no training 3/week for 8 weeks	100% adherence A, B, C ↑MIP, SMIP A ↑VC, TLC A, B ↑work capacity and power output All $p<0.01$ D no change
Kellerman et al. 2000	10 healthy	Single group Threshold device, 4 sets of 6 breaths, 10-15 second rest between breaths, 75%MIP (measured weekly) 5 days/week for 4 weeks 4 day habituation, supervised group training	No change in FVC, FEV_1 ↑ MIP $p<0.05$
Suzuki et al. 1993	12 healthy females	A Threshold device, 30%MIP, 15min/day, 2/day, 7days per week for 4 weeks Rest periods between sets not defined B control group no defined protocol	A no change in VC, FEV_1 after 4 weeks or Borg during exercise After 2 weeks: ↑MIP After 4 weeks ↑MIP, MEP, Pdimax (transdiaphragmatic pressure), ↑MVV All $p < 0.05$ B no change
Witt et al. 2007	16 healthy males	A 3 sets of 75 breaths at 50%MIP, 5 minute rest between sets B 3 sets of 75 breaths at 10%MIP, 5 minute rest between sets Threshold device 1/day, 6 days/week for 5 week	Adherence A 97%, B 88%, A ↑MIP $p < 0.05$, no change MEP B no change Change in MIP greater in A compared to B $p < 0.05$

Key to Table 46

FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
VC	Vital capacity
TLC	Total lung capacity
MIP	Maximal inspiratory pressure
MEP	Maximal expiratory pressure
SMIP	Sustained maximal inspiratory pressure
MVV	Maximal voluntary ventilation
IMT	Inspiratory muscle training
TIRE	Test of incremental respiratory endurance
$\dot{V}O_2max$	Maximal oxygen consumption
RPE	Rate of perceived exertion

Table 47 Studies related to trained healthy participants

Author	Participants	Intervention and comparison	Outcome
Goosey-Tolfey et al. 2010	16 wheelchair basketball athletes	A 30 breaths at 50% MIP, 2/day, B 60 breaths at 15% MIP, 1/day , 7 days/week for 5 weeks Threshold device	Adherence 63% A, 79%B A, B ↑MIP, MEP $p<0.03$, no differences between groups A, B no change in FVC, FEV_1, PEFR, MVV, sprint performance
Inbar et al. 2000	20 well trained endurance track athletes	A week 1-4 increasing resistance from 30% to 80% MIP, 5% per session, week 5-9 80% MIP with resistance adjusted weekly B no resistance Threshold device, no rest period defined 30 minutes, 1/day, 6days/week for 10weeks	A ↑MIP, respiratory muscle endurance $p<0.005$ B MIP, respiratory muscle endurance unchanged No change in FVC, FEV_1, VO_{2max} in A or B
Kwok and Jones 2009	16 recreational runners	A 30 breaths 2/day at 80% MIP week 1-2, 90% MIP week 3-6. 7 days/week for 6 weeks B 30 shoulder circumduction exercises 2/day 7 days/week for 6 weeks Rest period not defined Flow resistance device	A ↑MIP, ↓1.5K time trial $p<0.05$ No change in $\dot{V}O_{2max}$ in either group
Mickleborough et al. 2010	24 university recreational runners	A TIRE protocol 80% SMIP B TIRE protocol 30% SMIP C no training 3 days/week for 6 weeks	A ↑MIP, SMIP, maximal inspiratory power output, inspiratory muscle work capacity (IMWC), TLim, run time to exhaustion All $p<0.05$ B, C no change in above variables Improvements in A significantly better than B, C $p<0.05$

Author	Participants	Intervention	Outcome
Romer et al. 2002a	16 male road cyclists including 5 triathletes	Participants ranked by maximal inspiratory power, matched and assigned to A/B A 30breaths at 50% maximal inspiratory power, 2 /day B 60breathes 1/day 15% maximal inspiratory power Threshold device, rest period not defined 7days /week, for 6 weeks	Adherence 96%A 95%B A ↑P_0 (pressure at zero flow), maximal inspiratory flow, maximal inspiratory power, 20K, 40K time trial all $p<0.01$ B no change in ↑P_0 (pressure at zero flow), maximal inspiratory flow, maximal inspiratory power, 20K, 40K time trial
Romer et al. 2002b	16 male road cyclists including 5 triathletes	Participants ranked by maximal inspiratory power, matched and assigned to A/B A 30breaths at 50% maximal inspiratory power, 2 /day B 60 breathes 1/day 15% maximal inspiratory power Threshold device, rest period not defined 7days /week, for 6 weeks	Less change in P_0 and maximal relaxation rate in A compared to B $p<0.05$
Voliantis et al. 2001	14 female competitive rowers	A 30 breathes at 50%MIP 2/day, B 60 breathes at 15%MIP 1/day, 7days/week for 11weeks Threshold device, no rest period defined	Adherence 96-97% 4 weeks A ↑MIP $p<0.05$ 11 weeks A ↑MIP, P_{ETO2}, Improved 6 minute power test, 5K time trial $p<0.05$ B Improved 6 minute power test, 5K time trial $p<0.05$ Change in MIP, P_{ETO2}, 6 minute power test, 5K greater in A than B $p<0.05$

Author	Participants	Intervention and comparison	Outcome
Williams et al. 2002	7 university cross country runners	Single group 5-7 sets of 4-5 minutes of loaded breaths, 1-2 min rest per set Resistance 50%MIP increasing by 5%/week 25 minutes/day, 4-5day/week for 4 weeks Threshold device	↑MIP, breathing endurance time $p<0.05$ No change in lung volume, $\dot{V}O_{2\ max}$, endurance run time

Key to Table 47

FEV_1	Forced expiratory volume in 1 second	IMT	Inspiratory muscle training
FVC	Forced vital capacity	TIRE	Test of incremental respiratory endurance
MIP	Maximal inspiratory pressure	$\dot{V}O_2max$	Maximal oxygen consumption
MEP	Maximal expiratory pressure	Tlim	Respiratory endurance time
SMIP	Sustained maximal inspiratory pressure	P_{ETO2}	partial pressure of end tidal oxygen
MVV	Maximal voluntary ventilation		

Table 48 Systematic reviews on inspiratory muscle training in healthy people

Author	Title	Sources	Method	Results
Illi et al. 2012	Effect of respiratory muscle training on exercise performance in healthy individuals	MEDLINE, EMBASE, CINAHL inception to October 2011	Inclusion criteria: all languages; all studies including RMT intervention; endurance performance as outcome measure. Exclusion criteria: combined endurance and strength training; unloaded breathing exercise or breathing therapy; meta-analysis used only controlled studies 2 independent reviewers with a 3rd reviewer used if lack of agreement.	236 studies found, 46 studies included. Conclusion: Respiratory muscle training improves endurance exercise performance in healthy subjects with greater improvements in less fit individuals and in sports of longer durations.

Author	Title	Sources	Method	Results
HajGhanbari et al. 2013	Effects of respiratory muscle training on performance in athletes: A systematic review and meta-analysis	MEDLINE, CINAHL, SPORTDiscus, EMBASE Cochrane Central Register of Controlled Trials, PEDro, EBM reviews, gray literature	Inclusion criteria: Healthy athletes with no disability age 15-40; Study was RCT; study included outcomes of sport performance and respiratory muscle strength or endurance; published in English. Exclusion criteria: Subjects had physical impairment that interfered with exercise involving large muscle groups; healthy adults that were not elite/recreational athletes. 2 independent reviewers with a 3rd reviewer used if lack of agreement.	5,132 studies found, 21 studies included. Conclusion: Respiratory muscle training improves sport performance

Table 49 Systematic reviews on inspiratory muscle training in people with health conditions

a) Chronic obstructive pulmonary disease (COPD)				
Author	**Title**	**Sources**	**Method**	**Results**
Geddes et al 2005	Inspiratory muscle training in adults with chronic obstructive pulmonary disease: a systematic review	MEDLINE, CINAHL Inception to 2003	Inclusion Criteria: RCT or randomised cross-over trial; English language; adults > 18 years old; stable COPD; comparison of IMT to another comparison group Independently reviewed by 2 reviewers, with a 3rd reviewer used if lack of agreement.	274 studies found, 19 studies included that compared: IMT vs. sham; IMT vs. no intervention; two intensities of IMT; two modes of IMT. Conclusion: Targeted inspiratory resistive or threshold IMT significantly improves inspiratory muscle strength and endurance and decreases dyspnoea for adults with stable COPD.

Author	Title	Sources	Method	Results
Geddes et al 2008	Inspiratory muscle training in adults with chronic obstructive pulmonary disease: an update of a systematic review	MEDLINE, CINAHL 2003-2007 EMBASE Inception to 2007	Inclusion Criteria: RCT or randomised cross-over trial; English language; adults > 18 years old; stable COPD; comparison of IMT to sham IMT or no intervention, low versus high intensities of IMT, different modes of IMT. Independently reviewed by 2 reviewers, with a 3rd reviewer used if lack of agreement.	Additional 17 articles found, 6 studies met inclusion criteria. Sub group analysis completed on studies that specifically compared targeted, threshold or normocapnic hyperventilation IMT with sham IMT. Conclusion: Targeted inspiratory resistive, threshold or normocapnic hyperventilation IMT significantly increases inspiratory muscle strength and endurance, improves outcomes of exercise capacity, quality of life as measured by chronic respiratory disease questionnaire and decreases dyspnoea in adults with stable COPD

Author	Title	Sources	Method	Results
Gosselink et al 2011	Impact of inspiratory muscle training in patients with COPD: what is the evidence?	MEDLINE, CINAHL, Cochrane Central Register of Controlled Trials, EMBASE, PEDro and DocOnline. Inception to 2009 ATS and ERS congress CD-ROMs 2000-2008 No language restrictions	Inclusion criteria: randomized controlled trial; COPD patients with pulmonary function tests; inspiratory muscle training at an intensity of ≥30%MIP or respiratory muscle endurance training in a controlled manner; outcomes MIP, inspiratory muscle endurance, dyspnoea rating, 6- or 12-min walking distance (6/12MWD) and/or health-related quality of life (HRQoL). Independently reviewed by 2 reviewers.	Present search found 129 studies which were added to a previous search (Lotters et al. 2002) with 14 studies. 30 studies met inclusion criteria. Conclusion: IMT is an effective treatment modality in COPD patients to improve respiratory muscle strength and endurance, resulting in reductions of dyspnoea and improvement in functional exercise capacity and HRQoL. Patients with more advanced muscle weakness seem to be better responders, especially when IMT is in addition to general exercise training. Inspiratory muscle endurance training is less effective than strength training.

b) Cystic Fibrosis (CF)				
Author	**Title**	**Sources**	**Method**	**Results**
Reid et al 2008	Effects of inspiratory muscle training in cystic fibrosis: a systematic review	MEDLINE, EMBASE, CINAHL Inception to 2008 Restricted to English language	Inclusion criteria: Participants were >13 years of age; the study compared an IMT group to a sham IMT, no intervention or other intervention group; the study used a randomized controlled trial or cross-over design with an adequate washout. 2 independent reviewers	46 studies found, 2 met inclusion criteria Conclusion: Evidence supporting the benefit of inspiratory muscle training on improving inspiratory muscle function in people with cystic fibrosis is weak, and its impact on dyspnoea, exercise capacity and quality of life is unclear.

Author	Title	Sources	Method	Results
Houston et al 2011	Inspiratory muscle training for cystic fibrosis (Cochrane Review)	CF trials register which includes searches from: MEDLINE, EMBASE, CF Conferences, Also CINAHL, AMED, PEDro, BIOSIS previews, Science Direct, Scopus to 2005 Current controlled trials, UK national research register	Inclusion criteria: Randomised or quasi- randomised clinical controlled trials; people diagnosed with CF; any age; IMT compared with sham, no treatment or comparison of modes. 3 independent reviewers	265 studies found, 11 met inclusion criteria Conclusion: There is no evidence to suggest that IMT is either beneficial or not.

c) Asthma				
Author	**Title**	**Sources**	**Method**	**Results**
Ram et al 2009	Inspiratory muscle training for asthma (Cochrane Review)	Cochrane Central Register of Controlled Trials MEDLINE January 1966 to March 2002, EMBASE January 1985 to March 2002, CINAHL to March 2002 and the UK National Research Register of trials January 1982 to March 2002, on line respiratory journals and manufacturers of training devices to obtain trials.	Inclusion criteria: Randomised controlled trials of IMT vs sham or no device; Patients with stable asthma; 2 independent reviewers	62 studies found, 5 met inclusion criteria Conclusion: IMT seems to improve MIP and there is insufficient evidence to suggest that IMT could provide clinical benefit to patients with asthma.

Key to Table 48 & 49

RCT	Randomised controlled trial	MIP	Maximal inspiratory pressure
COPD	Chronic obstructive respiratory disease	6/12MWD	Six/twelve minute walk distance
CF	Cystic fibrosis	HRQ_oL	Health related quality of life
IMT	Inspiratory muscle training		

7.12 Intervention study aims and objectives

Inspiratory muscle weakness was a key finding from the observation study and represents decreased capacity of the respiratory muscle pump within the model of respiratory failure in people with HD, see Figure 43. The preceding reviews suggest that IMT can be used in people with neurodegenerative conditions and may improve inspiratory muscle strength and functional activities. The aim of the intervention study was therefore to explore the feasibility and benefit of inspiratory muscle training in people with HD.

7.12.1 Study objectives

The objective of the study was to:

- Investigate the feasibility and benefit of inspiratory muscle training as a potential management strategy for people with Huntington's disease.

The principle research question was:

- Is inspiratory muscle training a feasible method to increase respiratory muscle strength in people with Huntington's disease?

A further research question was:

- Does inspiratory muscle training improve functional tasks?

The null hypotheses for the study were:

H_{01} People with HD will not adhere to an inspiratory training programme as defined as completing less than 85% of the programme;

H_{02} Inspiratory muscle training does not improve respiratory muscle strength in people with HD;

H_{03} Inspiratory muscle training does not improve peak cough flow in people with HD;

H_{04} Inspiratory muscle training does not improve sit to stand in 30 seconds performance in people with HD.

8 Intervention study methods

8.1 Research design

The intervention study was based on the principles of a randomised controlled trial with qualitative data collected to evaluate feasibility of inspiratory muscle training in people with HD. Randomisation reduces the likelihood of bias in allocation to groups and the inclusion of a control group enhances the probability of making causal inferences. Participants were randomised to one of two groups, each group following the same intervention and support programme. The device was set to an inspiratory resistance known to have no training effect (Geddes et al. 2008) for the sham group and set to a resistance of 50% of maximal inspiratory pressure for the other group. The study lasted seven weeks and all assessments were carried out in the participant's home.

8.2 Participants

8.2.1 Inclusion criteria

(i) Genetically confirmed HD;

(ii) Capacity to give informed consent;

(iii) Inspiratory muscle strength <80% predicted;

(iv) Maintenance of a stable medical regime for 4 weeks prior to initiation of study and;

(v) Aged 18 years and older.

8.2.2 Exclusion criteria

(i) History of additional prior neurological condition, such as stroke;

(ii) Uncontrolled psychiatric symptoms;

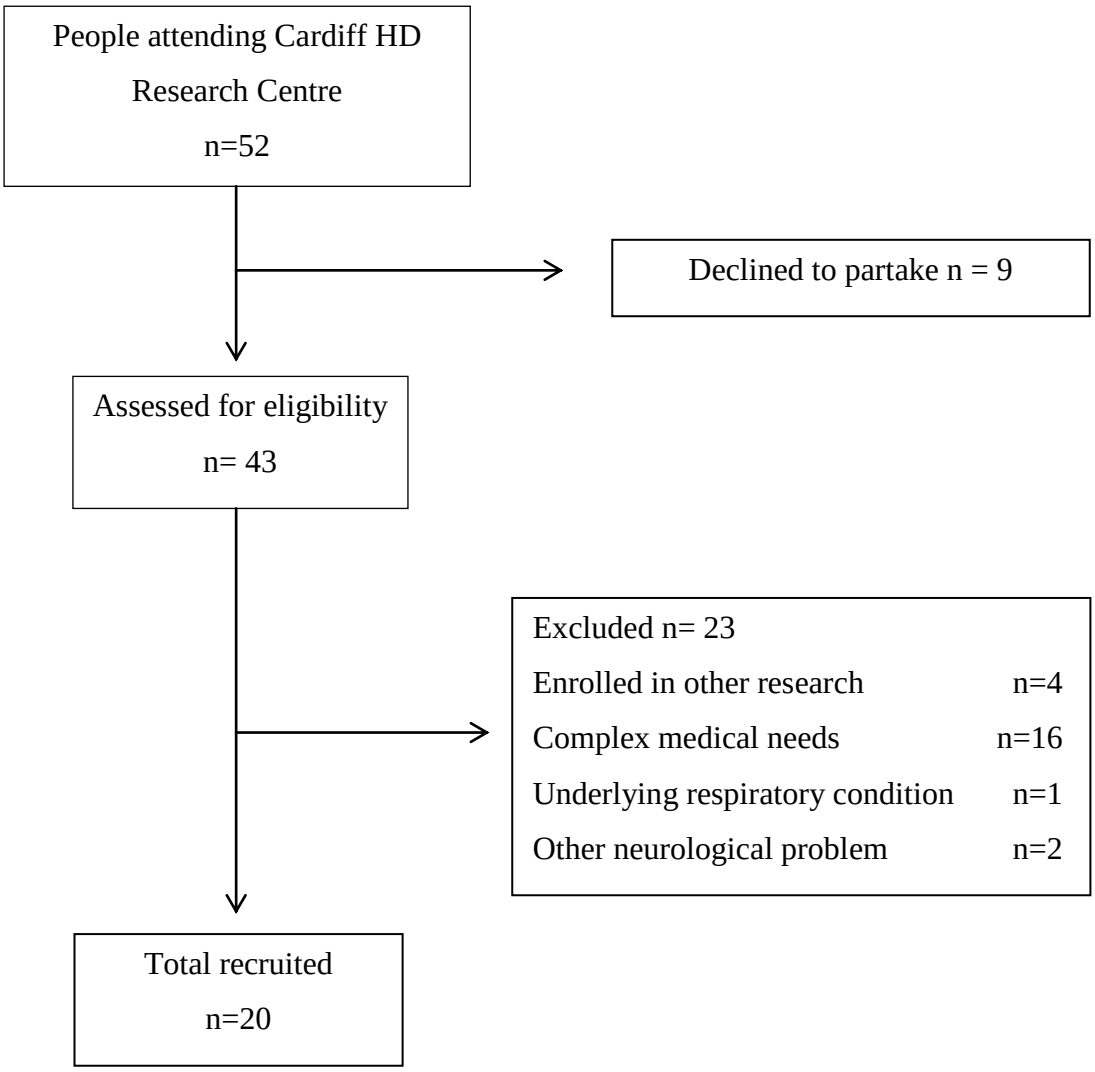
(iii) History of spontaneous pneumothorax/unstable asthma/chronic respiratory condition;

(iv) Unable to give consent.

8.2.3 Recruitment

Potential participants attending their routine clinic appointment were approached by Professor Anne Rosser, the clinician responsible for their care, and were invited to participate in the programme alongside the 'Registry' study as per the observation study, see section 4.6.4. The organisation of recruitment is summarised in Figure 46.

Figure 46 Intervention study recruitment flow chart

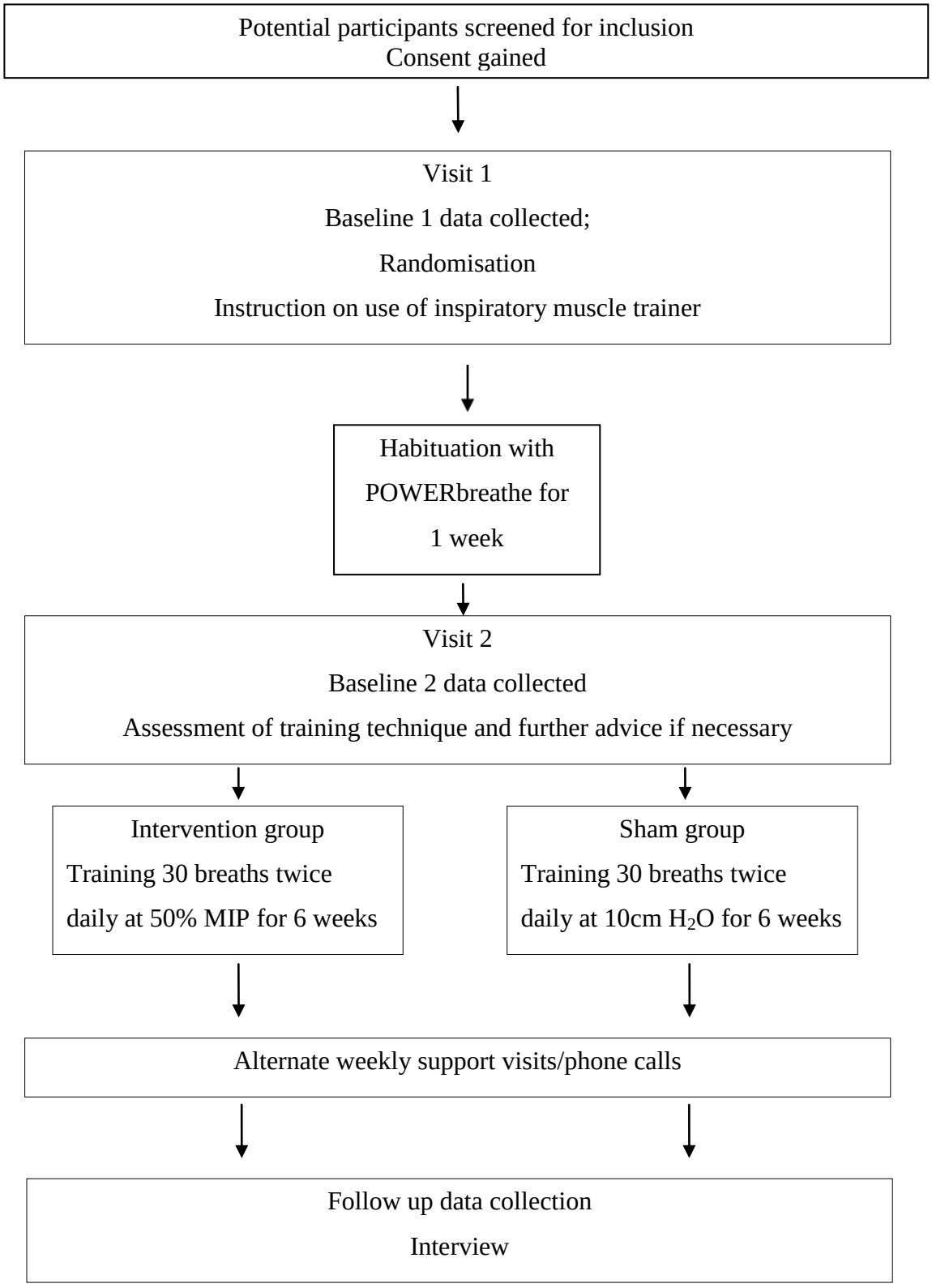


8.3 Intervention study protocol

The training programme used was based on previous research using the POWERbreathe device (Romer et al. 2002a; Volianitis et al. 2001). The POWERbreathe Kinetic 3 inspiratory muscle trainer was used, see appendix 4. This is a handheld device, with a variable valve which provides resistance throughout inspiration from residual volume to total lung capacity. It thus provides resistance throughout the available range of muscle work. The protocol, see Figure 47, required participants to use the training device for 30 breaths, twice a day, 7 days/week for 6 weeks. Resistance was set at 50% of maximal inspiratory pressure for the intervention group. Resistance was set at 10cmH_2O for the control group. This load is known to have no training effect and is used as a sham intervention (Geddes et al. 2008). The participants were not informed of their group allocation.

A habituation period of 1 week preceded the intervention phase, based on the method of Enright et al. (2006b). This enabled participants to familiarise themselves with the device and the training procedure. Baseline measures were also taken at the beginning of the habituation week to familiarise participants with the procedure. Support was provided throughout the study by alternating weekly phone calls and home visits. Further contacts were made available if necessary. Both groups were given the opportunity to keep the POWERbreathe device after the study.

Figure 47 Intervention study design protocol flow diagram



8.3.1 Randomisation

The sample was randomised using a minimisation method into two groups. With minimisation, allocation of the next participant enrolled is dependent upon the characteristics of those participants already enrolled. The advantage of minimisation in this pilot study is that there would be only minor differences between the groups in those factors used in the allocation process (Altman and Bland 2005). The three factors considered to have potential impact on the outcome of the study were age, gender and smoking (smoker/non-smoker) as the most important cause of COPD (Mannino and Buist 2007) and therefore influences respiratory function.

8.3.2 Measurement in the intervention study

This study explored the feasibility and benefit of inspiratory muscle training as a method to increase capacity of the respiratory muscle pump. The primary outcome measure was inspiratory muscle strength in order to investigate physiological changes in body structure and function. Inspiratory muscle strength was measured using sniff nasal inspiratory pressure (SNIP), as the testing manoeuvre is independent of the training manoeuvre, is reliable in healthy subjects (Maillard et al. 1998) and recommended for use in people with neurodegenerative conditions (Lofaso et al. 2006).

In the context of respiratory failure, cough efficacy is influenced by inspiratory muscle strength, as inspiratory muscle weakness results in small volumes of inhaled air, reducing expiratory pressure, flow and velocity (McCool 2006a). Measurement of cough efficacy by PCF was used in order to demonstrate any potential effect in a variable potentially related to type 1 respiratory failure.

As recommended by Polkey et al. (2011), a functional task was assessed. The 30 second sit to stand test is a valid field measure of lower body strength (Rikli and Jones 1999) and discriminates between different activity levels (Macfarlane et al. 2006). This was chosen due to its simplicity and the ability of the test to be carried out in the subjects' own homes.

Details of outcome measures are shown in Table 50. Standard operating procedures were utilised for conducting all outcome assessments, see Appendix 3.

The primary outcome measure to investigate physiological proof of principle of inspiratory muscle training in people with HD was inspiratory muscle strength measured as sniff nasal inspiratory pressure (SNIP). Previous studies on IMT have been criticised for using the same manoeuvre for assessment as is practised during the training programme i.e. a maximal

inspiration is used during training and used as the primary outcome measure and therefore participants may be just getting better at doing the test (Polkey et al. 2011). In this study SNIP was used as the outcome measure as it is a different manoeuvre to that used during training and is a valid measure of inspiratory muscle strength (Uldry and Fitting 1995). Maximal inspiratory pressure (MIP) was also measured as a complementary measure. Peak cough flow is recommended by the British Thoracic Society as a measure of cough efficacy in people with neuromuscular conditions (Bott et al. 2009). The 30 second sit to stand test was used to measure functional ability (Macfarlane et al. 2006).

Table 50 Outcome measures used in intervention study

Outcome measures B1 = first baseline; B2 = second baseline, 1 week after B1; F = follow up after 6 weeks intervention			
Domain to be measured	**Validated outcome measure**	**Time required**	**When**
Inspiratory muscle strength	Sniff nasal inspiratory pressure Maximal inspiratory pressure (ATS/ERS 2002)	5 minutes	B1;B2;F
Cough efficacy	Peak cough flow (Bott et al. 2009)	5 minutes	B1;B2;F
Functional task	30 second sit to stand (Macfarlane et al 2006)	5 minutes	B2;F

The outcome to measure adherence was the number of training sessions completed. These data are automatically stored and downloaded from the POWERbreathe K3 device and were recorded using a diary.

Acceptability of the intervention was assessed through interviews. A member of the research team, who was not the principle investigator, carried out the interviews in order to reduce bias, see appendix 7 for the interview schedule. The interview covered aspects including participant's views of the intervention, barriers and facilitators, impact of life events on adherence to the intervention, perception of benefit/non benefit and the importance of social support strategies.

8.4 Data Analysis

8.4.1 Sample size

Formal sample size calculations were not conducted. Twenty participants in total (10 per group) would however be sufficient to detect a standardised difference of 1.2 at the final measurement point, with a power of 80% and alpha level of 0.05.

8.4.2 Analysis of data

Adherence data collected from the device were compared to categories described by Fry et al (2007): full compliance >85% completion; partial compliance 70-84% completion; poor compliance 50-69% completion and non-compliant 10-49% completion.

Single case analysis included a summary of notes taken through the study and individual outcomes. Group data analysis included descriptive analysis using means, standard deviations, 95% confidence intervals and effect size.

Data from the interviews were transcribed and analysed using qualitative description method incorporating thematic content analysis. Qualitative description provides a rich straight description of a person's experience enabling researchers to stay close to the data collected (Neergaard et al. 2009). This was an appropriate method to analyse the semi structured interview as the aim was to gain an understanding of the participant's experiences in relation to acceptability of intervention. Thematic analysis was used following the method of Braun and Clarke (2006) using the following steps: transcription and reading of the data; generation of initial codes; creating potential themes; themes checked in relation to initial codes; naming of themes and generation of thematic map.

8.5 Ethical considerations

The general ethical considerations discussed in section 4.9 applied to the intervention study. Ethical approval was gained from the Research Ethics Committee for Wales 11/WA/0183, Cardiff and Vale University Health Board gave research and development approval as a patient identification centre for the intervention study (11-IBD-5200) and Cardiff University acted as sponsor (SPON 975-11), see Appendix 2.

Specific considerations for the intervention study were as follows.

8.5.1 Increased burden on participants

The main burden for participants participating in this research was their time. The intervention study required training for approximately 5 minutes, twice daily for 6 weeks. The data collection took approximately 2 hours in total.

8.5.2 Risk associated with inspiratory muscle training.

There is low risk associated with inspiratory muscle training, calculated as possible in likelihood and insignificant in consequence. Participants may feel some discomfort during training, but this would not cause any harm. This was explained to the participants during the

initial visit. All participants were able to keep the training device after the study was completed.

8.5.3 Project management

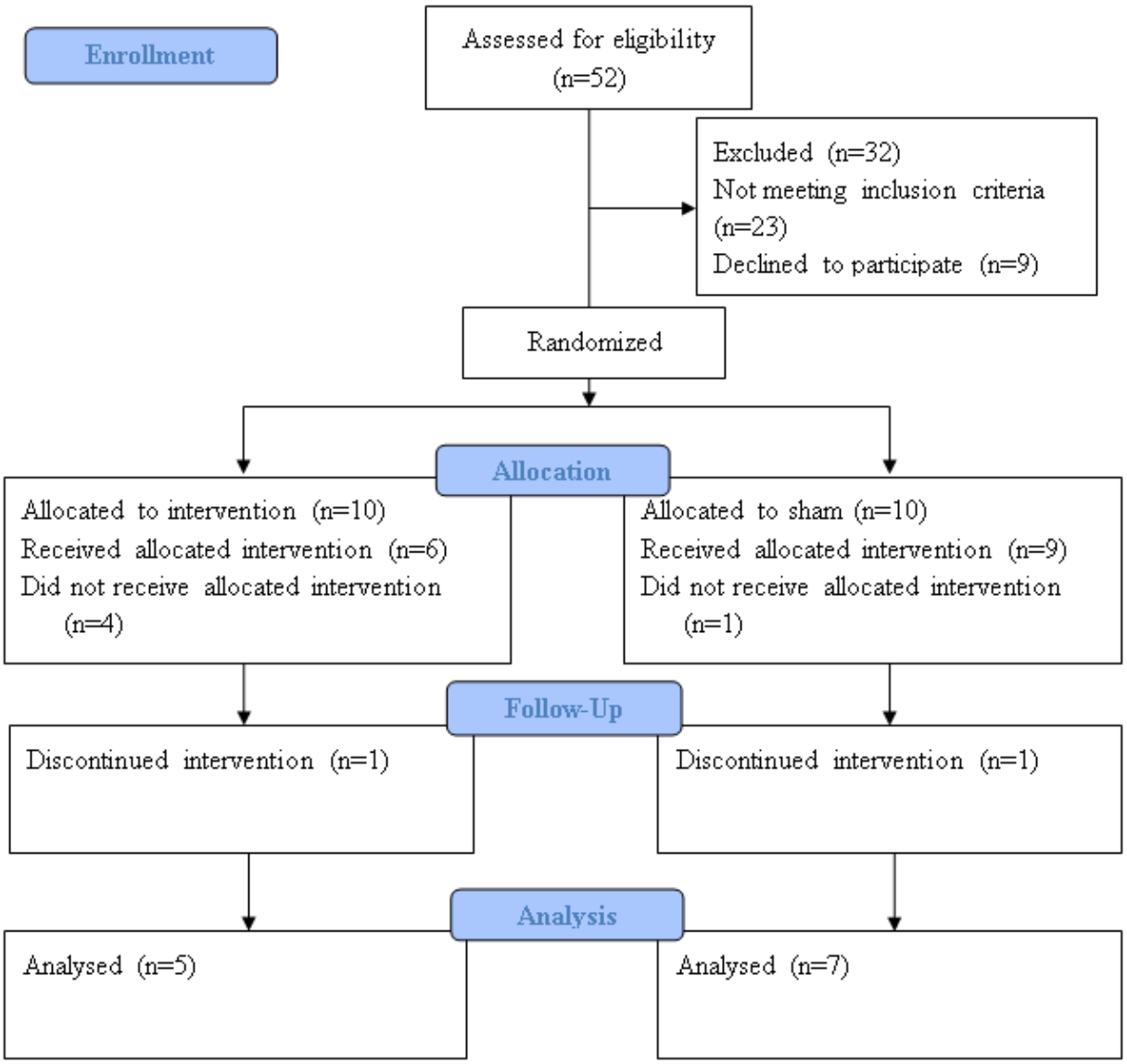
The project was primarily managed through the supervisory team of Dr Enright and Professor Busse who have specialist knowledge in inspiratory muscle training and HD respectively. A Study Steering Committee (SSC) consisting of the researcher, both supervisors and two independent members was established for the intervention study. The first meeting was held before the study commenced to review the protocol and arrange the timelines for subsequent meetings. The SSC provided overall supervision for the study and provided advice through its independent chair. The ultimate decision for the continuation of the study lay with the SSC.

9 Intervention study results

9.1 Participants

The participants who met the inclusion criteria for the study were randomised, and completed or did not complete the intervention study as described in Figure 48. A habituation period of one week preceded the intervention phase of the study. Reasons for not beginning the intervention were: inability to generate sufficient flow to use device (n=1); inability to co-ordinate limb and oral movements (n=1); inability to co-ordinate breathing and use of the device (n=2) and did not wish to continue (n=1). Two participants did not complete the study, reasons were: did not wish to continue (n=1); and other health issues prevented completion (n=1). One participant in the sham group did not withdraw from the study but did not complete the training as per protocol and therefore was withdrawn from analysis.

Figure 48 CONSORT flow diagram for intervention study



9.2 Demographic data

The demographic data for all participants enrolled into the intervention group are displayed in Table 51.

Table 51 Demographic data for participants recruited to intervention study

	Intervention	Sham
Age (years)	53.8 ±17.50	53.5 ±13.08
Gender	3F 7M	3F 7M
Smoker	7Sm 3NSm	7Sm 3NSm
MIP% Predicted	46.37 ±25.09	42.81 ±18.41
UHDRS:TMS	51.5 ±16.18 Range 20-72	58.8 ±17.69 Range 36-84
TFC	4.4 ±2.12 Range 2-9	6.4 ±3.17 Range 3-11
UHDRS:Cog	132.67 ±53.13 Range 64-207 n=6	151.33 ±54.85 Range 65-225 n=9

Gender	F=female, M=male
Smoker	Sm=smoker, NSm=non-smoker
MIP% Predicted	Maximal inspiratory pressure as a percentage of predicted
UHDRS:TMS:	Unified Huntington's disease rating scale: total motor score
TFC	Total functional capacity
UHDRS:Cog:	Unified Huntington's disease rating scale: cognitive score

The groups were matched for age, gender and smoking habit, as per minimisation protocol. The intervention group had a slightly lower UHDRS:TMS score, a lower TFC score and lower cognitive score, although the differences were not statistically significant. However, the mean cognitive score for the intervention group is categorised as markedly impaired whereas the mean score for the sham group is categorised as mildly impaired. The demographic data was explored further in respect of completers and drop outs, see Table 52 The demographic data for the sham group were similar for completers and drop outs. People who dropped out from the intervention group tended to have weaker inspiratory muscle strength, higher UHDRS: TMS scores, lower TFC scores yet higher cognitive scores.

Table 52 Demographics of drop outs and completers

	Intervention drop outs	Intervention completers	Sham drop outs	Sham completers
Age (years)	55 ±12.04	52.6 ±23.24	52.33 ±8.33	54.00 ±15.25
Gender	3F, 2M	5M	2F, 1M	1F, 6M
Smoker	3Sm, 2NSm	4Sm, 1NSm	2Sm, 1NSm	5Sm, 2NSm
MIP% Predicted	33.10 ±17.63	59.65 ± 25.80	47.62 ±34.05	40.75 ±10.26
UHDRS:TMS	59.20 ±15.07	43.80 ±14.62	60.33 ±17.01	58.14 ±19.27
TFC	3.6 ±1.52	5.20 ±2.49	6.33 ±3.51	6.43 ±3.31
UHDRS:Cog	151.33 ±76.58 (n=3)	114 ±12.17 (n=3)	140.67 ±53.98 (n=3)	156.67 ±59.54 (n=6)

MIP Maximal inspiratory pressure (cmH_2O)
UHDRS:TMS: Unified Huntington's disease rating scale: total motor score
TFC Total functional capacity
UHDRS:Cog: Unified Huntington's disease rating scale: cognitive score

9.3 Individual analysis of data from intervention study

The number of participants within the study was small and therefore analysis was carried out on both an individual and group basis. Individual profiles of all participants are presented followed by group analysis of participants who completed the study as per protocol.

9.3.1 Subject 01: sham group

Subject 01 was a 67 year old male who was a non-smoker and lived with his wife. His TFC score was 4, UHDRS:TMS 62 and a cognitive score of 65. His adherence was 94% as recorded in the diary and 37% as recorded by the device. The reason for non-adherence was forgetting to do the exercises. Study data show an increase in MIP, a decrease in SNIP and PCF and no change in sit to stand see Table 53. The training load was consistent at 10cmH_2O throughout the study, providing approximately 42% MIP resistance.

Table 53 Subject 01 study data

	Baseline 1	Baseline 2	Final	Change final – baseline 2
SNIP (cmH_2O)	35	35	34	-1
MIP (cm H_2O)	24	24	26	2
PCF (L/min)	170	296	291	-5
Sit-stand		6	6	0

SNIP Sniff nasal inspiratory pressure (cmH_2O)
MIP Maximal inspiratory pressure (cmH_2O)
PCF Peak cough flow (litres/minute)

Facilitators, barriers and perceived benefits of the training programme

The following data were collected by interview and study notes written during the researcher's visits. The main facilitator for the training programme was the subject's wife. Although the subject was independent in using the device and finding it easy to use, the subject's wife cleaned and assembled it and reminded the subject to do the exercises. The disparity between the diary and device adherence data is not clear, but it may be that the subject was not actually turning the device on. He complained of not being able to see the image on the device during training and on reviewing the technique, the subject turned the device on but did not press the start button. The technique was reviewed at each visit. The subject's wife felt that the home visits were valuable for getting feedback from the researcher, although the number of visits could have been reduced. The subject and his wife felt no appreciable benefit to the training; it was felt that although walking distance and breathlessness had improved, this may have been due to generally feeling better than in the recent past. It was felt that speech was worse. The wife valued the research study and said that they liked to get involved in studies.

9.3.2 Subject 02: sham group

Subject 02 was a 67 year old male who was a non-smoker and lived with his wife. His TFC score was 11, UHDRS:TMS 41 and cognitive score 201. Adherence was 95% as recorded in the diary and 86% recorded by the device. Reasons for non-adherence: busy x2 (preparing Sunday dinner; watching rugby) too tired; device needed to be charged. The researcher noted some issues with the device recording sessions. The study data show an increase in MIP and PCF and a decrease in SNIP and sit to stand, see Table 54. The training load was consistent at $10cmH_2O$ throughout the training study, providing approximately 17.5%MIP resistance.

Table 54 Subject 02 study data

	Baseline 1	Baseline 2	Final	Change final -baseline 2
SNIP (cmH_2O)	24	43	31	-12
MIP (cm H_2O)	49	57	76	19
PCF (L/min)	343	279	442	163
Sit-stand		11	10	-1

SNIP Sniff nasal inspiratory pressure (cmH2O)
MIP Maximal inspiratory pressure (cmH2O)
PCF Peak cough flow (litres/minute)

Facilitators, barriers and perceived benefits of the training programme

The following data were collected by the researcher as study notes written during visits. The only issue raised by the subject, was some difficulty in maintaining a seal around the mouthpiece of the device. The main enabler was creating a routine with the main barrier being finding time to do the exercises. The subject did not perceive any benefit for the training.

9.3.3 Subject 03: intervention group

Subject 03 was a 44 year old female who was a non-smoker who lived with her husband and had full time care when her husband was at work. Her TFC score was 2 and UHDRS:TMS 72. She was unable to undertake training as she was unable to generate sufficient volume and flow to trigger the device. Her baseline 1 readings were SNIP 15cmH_2O, MIP 11cmH_2O and PCF 196 L/min.

9.3.4 Subject 04: sham group

Subject 04 was a 55 year old male who smoked and lived alone; he had support from community nursing care for the study. His TFC score was 3, UHDRS:TMS 67 and cognitive score 109. The subject withdrew from the study during the habituation week as he found the intervention too complex and that this increased his anxiety. The community nurse felt that motivation was an issue and that the subject was unable to learn the skill of using the device, particularly in the mornings when the subject found it difficult to co-ordinate and process new information. His baseline 1 readings were SNIP 28cmH_2O, MIP 16cmH_2O and PCF 217L/min.

9.3.5 Subject 05: intervention

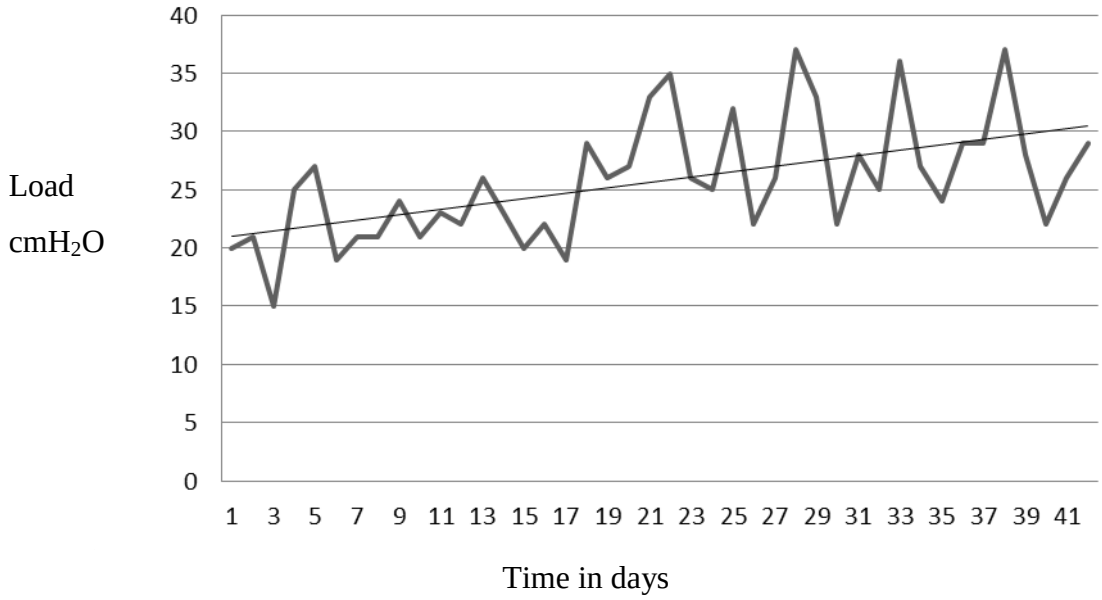
Subject 05 was an 80 year old male who was a non-smoker and lived with his wife. His TFC score was 3 and UHDRS:TMS 59. His adherence was 52% as recorded by the diary and 49% recorded by the device. Reasons for non-adherence were: unwell x8, tired x7, at daycare/respite x13, needed charging x1, missed x10. Study data show an increase in SNIP but decrease in MIP and PCF, with no change in sit to stand, see Table 55. The data collected from the device during the intervention demonstrated an upward trend in resistance provided by the device Figure 49. Resistance was set at 50% of MIP, which was measured during the first two breaths of the training session. From the beginning to the end of the intervention, resistance increased by approximately 10cmH_2O, indicating an increase in the daily MIP values.

Table 55 Subject 05 study data

	Baseline 1	Baseline 2	Final	Change final – baseline 2
SNIP (cmH_2O)	29	12	19	7
MIP (cm H_2O)	50	73	48	-25
PCF (L/min)	351	476	436	-40
Sit-stand		4	4	0

SNIP Sniff nasal inspiratory pressure (cmH_2O)
MIP Maximal inspiratory pressure (cmH_2O)
PCF Peak cough flow (litres/minute)

Figure 49 Subject 05: Resistance provided by device during each day of training



Facilitators, barriers and perceived benefits of the training programme

The following data were collected by interview and study notes written during the researcher's visits. The main facilitator was the subject's wife who cleaned and assembled the device and prompted the subject to do the exercises. The subject carried out the exercises independently, but often required input from his wife to co-ordinate breathing in and breathing out. His wife felt that if she was not there, that the subject may not carry out the exercises. During a visit the researcher noted that the subject was rushing the technique and therefore advice was given on slowing down and concentrating on full in and full out breaths. There were some issues with the device not recording breaths, but this seemed to resolve when the frequency of breathing was reduced. The subject felt that stair climbing was better since starting the exercises.

9.3.6 Subject 06: sham group

Subject 06 was a 54 year old female who was a non-smoker and lived with her husband and was in a stable gym exercise routine. Her TFC score was 6, UHDRS:TMS 47 and cognitive score of 160. Adherence was 100% as recorded in the diary and 98% recorded on the device. Study data show increases in SNIP, MIP, PCF and no change in sit to stand see Table 56. The training load was consistent at 10cmH_2O throughout the study, providing approximately 20%MIP resistance.

Table 56 Subject 06 study data

	Baseline 1	Baseline 2	Final	Change final – baseline 2
SNIP (cmH_2O)	40	44	45	1
MIP (cm H_2O)	30	49	59	10
PCF (L/min)	394	357	412	55
Sit-stand		11	11	0

SNIP Sniff nasal inspiratory pressure (cmH_2O)
MIP Maximal inspiratory pressure (cmH_2O)
PCF Peak cough flow (litres/minute)

Facilitators, barriers and perceived benefits of the training programme

The following data were collected by the researcher as study notes written during visits. The subject carried out the training programme independently and had no problems during the study. She did not notice any change in activities of daily living, cough or speech as a consequence of the training. She felt that the training was not difficult and that it was something that she may do later on to maintain her breathing.

9.3.7 Subject 07: intervention group

Subject 07 was a 60 year old male who was a non-smoker who lived at home with his wife and two children. His TFC score was 3, UHDRS:TMS 68 and cognitive score of 64. At the first visit, the subject had difficulties in co-ordinating breathing and using the device as he had facial and upper limb chorea. He was willing to carry on with the study at this point, but after a few days the subject's wife felt that the intervention was too difficult to continue due to co-ordination problems. The co-ordination problems were both in pattern of breathing and chorea. The subject's motivation to continue was also low. His baseline readings were: SNIP 33cmH_2O, MIP 27cmH_2O and PCF 122L/min.

9.3.8 Subject 08: sham group

Subject 08 was a 45 year old male who was a non-smoker and lived with his wife and child. His TFC score was 3 and UHDRS:TMS was 83. Adherence recorded in the diary was 71.4% and 83.2 % recorded by the device. Reasons for non-adherence were going out x4; no reason x3; busy x2; hospital appointment x1; forgot x1; father's day x1. The study data show an increase in SNIP and PCF. The change in PCF was based on final-baseline 1, as the subject

was unable to give full effort at baseline 2. MIP and sit to stand decreased, see Table 57. The training load was consistent at 5cmH_2O, providing approximately 7%MIP resistance.

Table 57 Subject 08 study data

	Baseline 1	Baseline 2	Final	Change final – baseline 2
SNIP (cmH_2O)	62	70	80	10
MIP (cm H_2O)	37	69	67	-2
PCF (L/min)	250	77 Unable to get full effort	388	Final-baseline 1 138
Sit-stand		21	19	-2

SNIP Sniff nasal inspiratory pressure (cmH_2O)
MIP Maximal inspiratory pressure (cmH_2O)
PCF Peak cough flow (litres/minute)

Facilitators, barriers and perceived benefits of the training programme

The following data were collected by interview and study notes written during the researcher's visits. The main facilitator was the subject's wife who prompted the use of the device and coached during the exercise. The exercises were short, compared to other exercise studies and easy to do. Having a routine facilitated carrying out the exercise, and this was better in the morning compared to evening, when the subject got tired. During the researcher's visits, it was noted that the subject took successive short inspirations before expirations. Following coaching from the researcher during the visit and wife during the intervention, the number of multiple breaths reduced, and inspirations were slower and longer. The subject's wife felt that his swallow had improved since the intervention. Barriers tended to be family events and tiredness in the evening. The device was easy to use, but not something that they would take out with them.

9.3.9 Subject 09: intervention group

Subject 09 was a72 year old female who smoked and lived with her partner. Her TFC score was 4 and UHDRS:TMS 52. The subject had difficulty in performing the technique due to problems with co-ordinating her breaths with using the device, poor seal around the mouthpiece and was unable to activate the device. This caused increased frustration and anxiety and the subject withdrew from the study. Her baseline data were SNIP 18cmH_2O, MIP 13cmH_2O and PCF 101L/min.

9.3.10 Subject 10: sham group

Subject 10 was a 59 year old female who was a non-smoker and lived alone and had social support. She had a TFC of 6, UHDRS:TMS of 73 and cognitive score of 110. She did not complete the diary and her adherence was 1.2% as recorded by the device. She carried out 1 training session in 6 weeks with the researcher, but was always happy to try and continue with the study. The reason for not completing training was hay fever. It was noted during the researcher's visits that the subject had difficulties using the device. Initially, she had difficulties pressing the buttons to start the training, but this improved in subsequent visits. She had difficulties co-ordinating breaths with using the device, often expiring instead of inspiring through the device. There were difficulties with the flange, as it sometimes came off during a breathing manoeuvre. The researcher removed the flange and the subject felt that this was easier to use. The researcher noted that the subject had decreased ability to follow instructions but always consented to carrying on with the study. The data were collected, see Table 58 but not used in the group analysis as the intervention had not been followed as per protocol. SNIP, MIP, PCF and sit to stand all increased

Table 58 Subject 10 study data

	Baseline 1	Baseline 2	Final	Change final – baseline 2
SNIP (cmH_2O)	42	39	65	26
MIP (cmH_2O)	31	29	40	11
PCF (L/min)	263	208	257	49
Sit-stand		8	9	1

SNIP Sniff nasal inspiratory pressure (cmH_2O)
MIP Maximal inspiratory pressure (cmH_2O)
PCF Peak cough flow (litres/minute)

9.3.11 Subject 11: intervention group

Subject 11 was a 28 year old male who smoked and lived with his parents. His TFC score was 3, UHDRS:TMS 51 and cognitive score of 100. Adherence as recorded by the diary was 36% and 63% as recorded by the device. Reasons for non-adherence were that the subject was asleep x4. The subject smoked through a home-made device that included a 5mm wide and 95cm long tube. Study data show an increase in MIP, PCF and sit to stand and a decrease in SNIP see Table 59. The resistance provided by the device showed an upward trend of

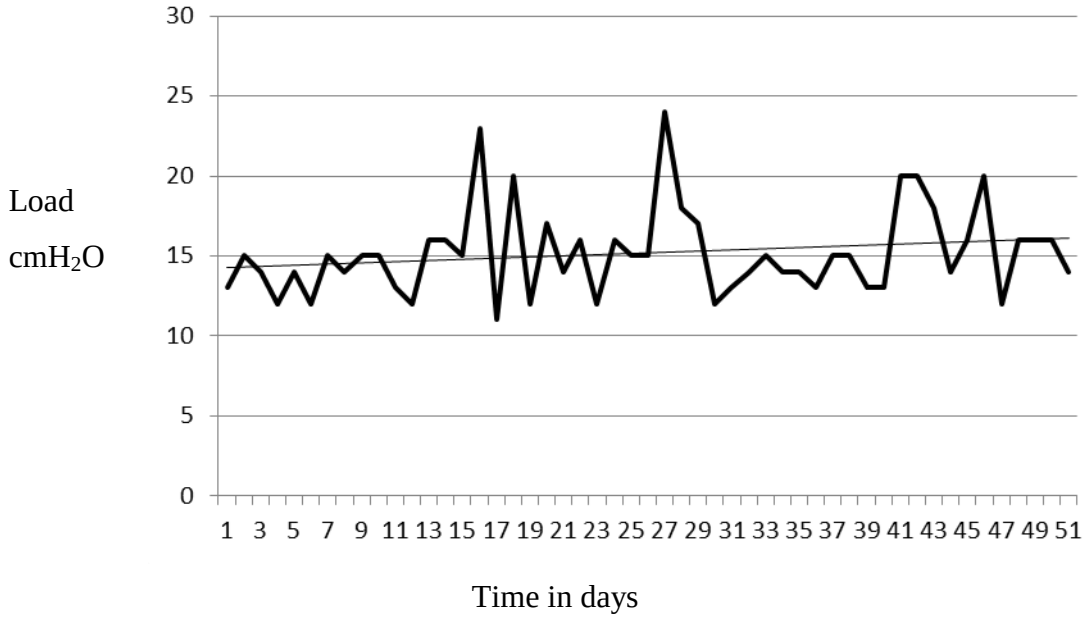
approximately 2cmH_2O across the study, indicating change in daily MIP measures, see Figure 50.

Table 59 Subject 11 study data

	Baseline 1	Baseline 2	Final	Change final - baseline 2
SNIP (cmH_2O)	24	42	37	-5
MIP (cm H_2O)	44	38	41	3
PCF (L/min)	n/a	213	313	100
Sit-stand		9	10	1

SNIP Sniff nasal inspiratory pressure (cmH_2O)
MIP Maximal inspiratory pressure (cmH_2O)
PCF Peak cough flow (litres/minute)

Figure 50 Subject 11: Resistance provided by device during each day of training



Facilitators, barriers and perceived benefits of the training programme

The following data were collected by interview and study notes written during the researcher's visits. The main facilitator was the subject's father, who cleaned, assembled and supervised the exercises. The flanged mouthpiece was a major obstacle to the exercises being carried out and this was adapted by removing the lugs at each side, resulting in an oval tube. This was somewhat satisfactory, but the subject did tend to bite down on the tube. There were

some difficulties with co-ordination of breathing with the device, with the subject sometimes not generating sufficient flow to trigger the device. This improved when the subject was sat up in bed, this position also offered less distraction from TV and computer screens. The device did not appear to hold power and therefore advice was given on charging the device overnight rather than just for a few hours. The subject's father felt that the weekly phone calls/visits were helpful to discuss adaptations to the device and that training once a day may be better than twice, as it was sometimes difficult to fit in two sessions. The subject's mother commented that the parent/child relationship was sometimes difficult, as the onus was on them to remember to do the exercises and there was an element of guilt if they forgot. The parents did not observe any perceived benefit from the exercises.

9.3.12 Subject 12: intervention group

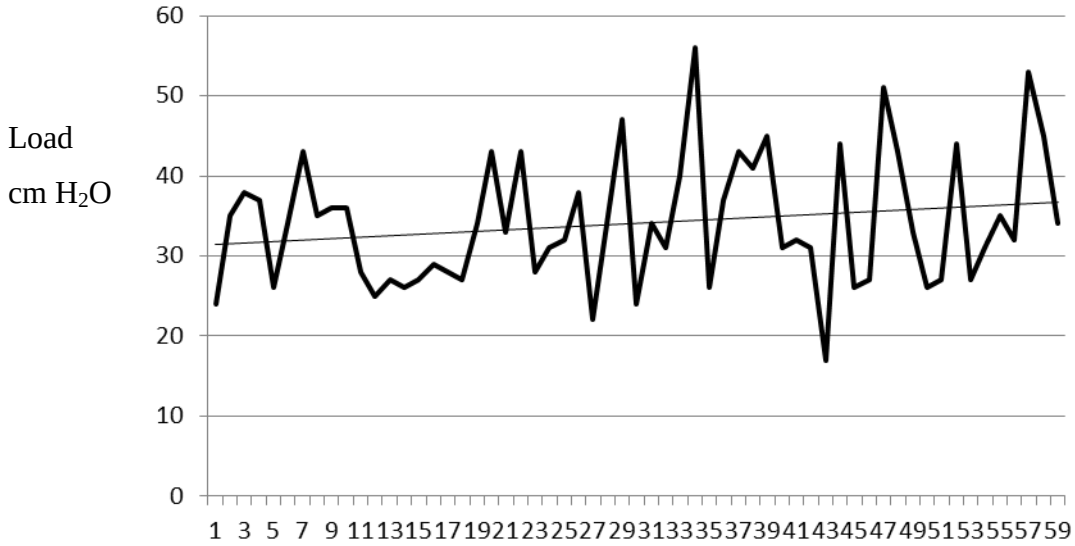
Subject 12 was a 31 year old male who was a non-smoker who lived alone. His TFC score was 9 and UHDRS:TMS 20. Adherence as recorded by the device was 77%, a diary was not kept. Reasons for non-adherence were being busy or away from home. Study data show an increase in SNIP, MIP and PCF with no change in sit to stand, see Table 60. The resistance provided by the device increased by approximately 5cmH_2O across the intervention period, indicating an increase in daily MIP values, see Figure 51.

Table 60 Subject 12 study data

	Baseline 1	Baseline 2	Final	Change final - baseline 2
SNIP (cmH_2O)	64	64	67	3
MIP (cmH_2O)	74	85	105	20
PCF (L/min)	548	567	649	82
Sit-stand		15	15	0

SNIP Sniff nasal inspiratory pressure (cmH_2O)
MIP Maximal inspiratory pressure (cmH_2O)
PCF Peak cough flow (litres/minute)

Figure 51 Subject 12: Resistance provided by device during each day of training



Facilitators, barriers and perceived benefits of the training programme

The following data were collected by interview and study notes written during the researcher's visits. The main facilitator for the intervention was setting an alarm to remind the subject when to carry out the exercises. It helped having the researcher come and review the exercises, although there were no difficulties in carrying them out. There were some problems with the device: it took a long time to charge and the buttons were not intuitive. The subject lost the flange, but continued using the device without this. The subject did not notice any benefit from the exercise. He was happy to do the study and thought that if the outcome of the study was positive, then he would continue with the exercises.

9.3.13 Subject 13: sham group

Subject 13 was a 41 year old male who smoked and lived in a care home facility. His TFC score was 4, UHDRS:TMS 84 and cognitive score 110. Adherence as recorded by the diary was 58.3% and 75% as recorded by the device. Reasons for non-adherence were: nursing staff forgot; not awake long enough for 2 sessions x2; refused x1; machine not working correctly. During baseline 1, the subject had difficulty coughing into the mouthpiece and a face mask was used for baseline 2 and final measures. Subsequent to this, a reliability and validity study was carried out which showed that PCF using face mask was valid as compared to mouthpiece and reliable in healthy subjects (Jones et al. 2013). Study data show an increase in SNIP and PCF and decreases in MIP and sit to stand, see Table 61. The

baseline 2 SNIP ready was considerably lower than baseline, the reason for this is not known. The final sit to stand measure was reduced as the subject stopped to pull up his trousers. As the subject was busy, the test was not repeated. The training device provided a consistent load of 5cmH_2O throughout the study, providing approximately 12%MIP resistance.

Table 61 Subject 13 study data

	Baseline 1	Baseline 2	Final	Change final – baseline 2
SNIP (cmH_2O)	38	14	60	46
MIP (cmH_2O)	35	41	39	-2
PCF (L/min)	107	329*	372	43
Sit-stand		14	10**	-4

*Measuring device altered from mouthpiece to face mask
** stopped to pull up trousers
SNIP Sniff nasal inspiratory pressure (cmH_2O)
MIP Maximal inspiratory pressure (cmH_2O)
PCF Peak cough flow (litres/minute)

Facilitators, barriers and perceived benefits of the training programme

The following data were collected by interview and study notes written during the researcher's visits. The main facilitator was the support from the care home staff. The staff cleaned and assembled the device and the subject reminded staff about carrying out the exercises. The carers felt that the subject would have been unable to assemble the device independently. There were some problems with co-ordination in terms of placing the device in the mouth and this was resolved by staff helping. There was also a problem with the flange and the researcher advised using the device without the flange. There were some problems with charging the device and advice was given to charge overnight. The subject felt that his swallowing was better since carrying out the exercises.

9.3.14 Subject 14: sham group

Subject 14 was a 72 year old male who did not smoke and lived with his wife. His TFC score was 6, UHDRS:TMS 54 and cognitive score 225. Adherence as recorded by the diary was 83% and 67.9% as recorded by the device. No reasons were given for non-adherence. Study data show that SNIP increased, MIP and PCF decreased and no change in sit to stand, see Table 62. The training load provided by the device was consistent at 10cmH_2O throughout the study, providing approximately 30%MIP resistance.

Table 62 Subject 14 study data

	Baseline 1	Baseline 2	Final	Change final – baseline 2
SNIP (cmH_2O)	56	44	51	7
MIP (cmH_2O)	332	33	24	-9
PCF (L/min)	184	277	217	-60
Sit-stand		7	7	0

SNIP Sniff nasal inspiratory pressure (cmH_2O)
MIP Maximal inspiratory pressure (cmH_2O)
PCF Peak cough flow (litres/minute)

Facilitators, barriers and perceived benefit of the training programme

The following data were collected by interview and study notes written during the researcher's visits. The main facilitator was keeping the device in view in order to remember to carry out the exercises. It was noted on the baseline 2 visit that the device was not being used correctly as the subject was not pressing the start button twice. Advice was given and reminders written in the diary. The device had been dropped and the posterior valve broke, this was replaced and training continued. The subject tended to breathe very quickly and sometimes there was more emphasis on expiration rather than inspiration, advice on correct technique was given by the researcher. The subject did not perceive any benefit from the study.

9.3.15 Subject 15: sham group

Subject 15 was a 32 year old male who smoked and lived with his mother. His TFC score was 11, UHDRS:TMS 36 and cognitive score 179. Adherence as recorded by the device was 66.7%, a diary was not kept. The study data show an increase in MIP and decreases in SNIP, PCF and sit to stand see

Table 63. The resistance provided by the device was consistent at 10cmH_2O throughout the study, providing approximately 18%MIP resistance.

Table 63 Subject 15 study data

	Baseline 1	Baseline 2	Final	Change final – baseline 2
SNIP (cmH_2O)	44	72	70	-2
MIP (cmH_2O)	56	55	63	8
PCF (L/min)	563	550	473	-77
Sit-stand		14	13	-1

SNIP Sniff nasal inspiratory pressure (cmH_2O)
MIP Maximal inspiratory pressure (cmH_2O)
PCF Peak cough flow (litres/minute)

Facilitators, barriers and perceived benefit of the training programme

The following data were collected by the researcher as study notes written during visits. The main facilitator was setting a routine which fitted in with the subject's work times. The subject and his mother felt that the researcher's visits and phone calls were helpful. The device was easy to use, although the subject did not like the flange and used the device without it. The subject felt that his speech was better, in that people could understand him better, the words were clearer and sentences longer.

9.3.16 Subject 16: intervention group

Subject 16 was a 56 year old female who was a non-smoker and lived with her husband and son. Her TFC was 6, UHDRS:TMS 36 and cognitive score 207. The subject successfully carried out the exercises during baseline 1 and baseline 2 visits. The resistance was reduced from 50%MIP to 40%MIP as the subject was unable to trigger the device at the former resistance. At visit 1, the subject withdrew from the study as she felt that she could not "get into the training". The subject's baseline 2 data were: SNIP 32cmH_2O, MIP 37cmH_2O, PCF 331L/min and sit to stand 12.

9.3.17 Subject 17: intervention group

Subject 17 was a 71 year old male who was a non-smoker and lived with his wife. His TFC score was 5, UHDRS:TMS 43 and cognitive score 122. Adherence was 83% as recorded by the device, no diary was kept. The study data show that SNIP, MIP and sit to stand increased and PCF decreased see Table 64. Variable resistance was provided by the device during the intervention. On the baseline 2 visit, it was noted that the device was set at 80%MIP; this was adjusted to a level that the subject found capable of breathing against which was 40%. The

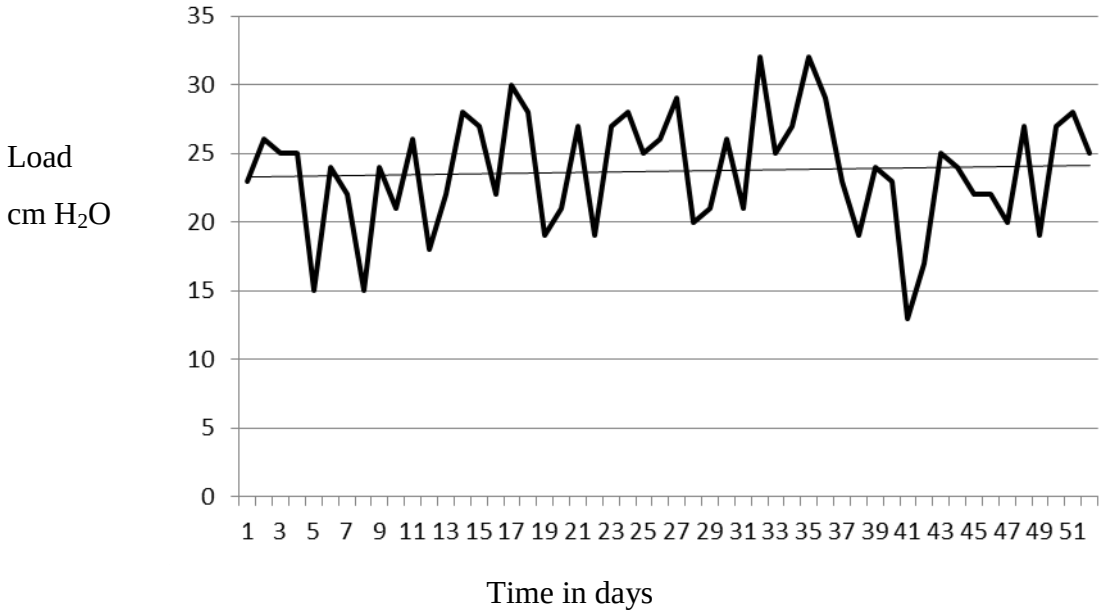
resistance was adjusted to 50% on visit 1, but on visit 2 was reduced to 40% as the subject found 50% too difficult. The resistance, in cmH_2O, provided by the device remained constant throughout the study see Figure 52 (baseline 2 to final visit).

Table 64 Subject 17 study data

	Baseline 1	Baseline 2	Final	Change final – baseline 2
SNIP (cmH_2O)	33	23	55	32
MIP (cmH_2O)	28	35	45	10
PCF (L/min)	116	306	296	-10
Sit-stand		4	7	3

SNIP Sniff nasal inspiratory pressure (cmH_2O)
MIP Maximal inspiratory pressure (cmH_2O)
PCF Peak cough flow (litres/minute)

Figure 52 Subject 17 Resistance provided by device during training programme



Facilitators, barriers and perceived benefits of the training programme

The following data were collected by interview and study notes written during the researcher's visits. The main facilitator was being reminded to do the exercise by the subject's wife, who also cleaned and assembled the device. The subject continued to use the device while away on holiday, but sometimes missed sessions due to family commitments. There were some problems with device not holding its charge and sometimes not recording

breaths. The subject had been on antibiotics for a chest infection in the habituation week. The subject did not perceive any benefit from the training programme.

9.3.18 Subject 18: intervention group

Subject 18 was a 43 year old man who was a smoker and lived in a care home facility. His TFC score was 3, UHDRS:TMS 68 and cognitive score 183. During baseline 1 visit, the subject had difficult in co-ordinating breathing with using the device, as he emphasised expiration rather than inspiration. At baseline 2 visit, the subject's technique had improved and he was happy to continue with the study. At the first phone call, the carer stated that the subject was having difficulty with the training and visit 1 was moved to an earlier date. At this visit, the subject withdrew from the study. The subject felt that it was too difficult to co-ordinate his breathing with using the device; the carer felt that the subject had low motivation and had other concerns in his life that needed his attention. Data from baseline 2 were SNIP 24cmH_2O, MIP 29cmH_2O, PCF 365L/min and sit to stand 8.

9.3.19 Subject 19: sham group

Subject 19 was a 43 year old female who was a smoker and lived alone. Her TFC score was 10, UHDRS:TMS 41 and cognitive score 203. The subject had a high breathing rate whilst carrying out the exercises and advice was to slow the rate and ensure full inspiration and expiration. At visit 1, the subject had other health issues and withdrew from the study. The baseline 2 data were SNIP 49cmH_2O, MIP 83cmH_2O, PCF 305L/min and sit to stand 14.

9.3.20 Subject 20: intervention group

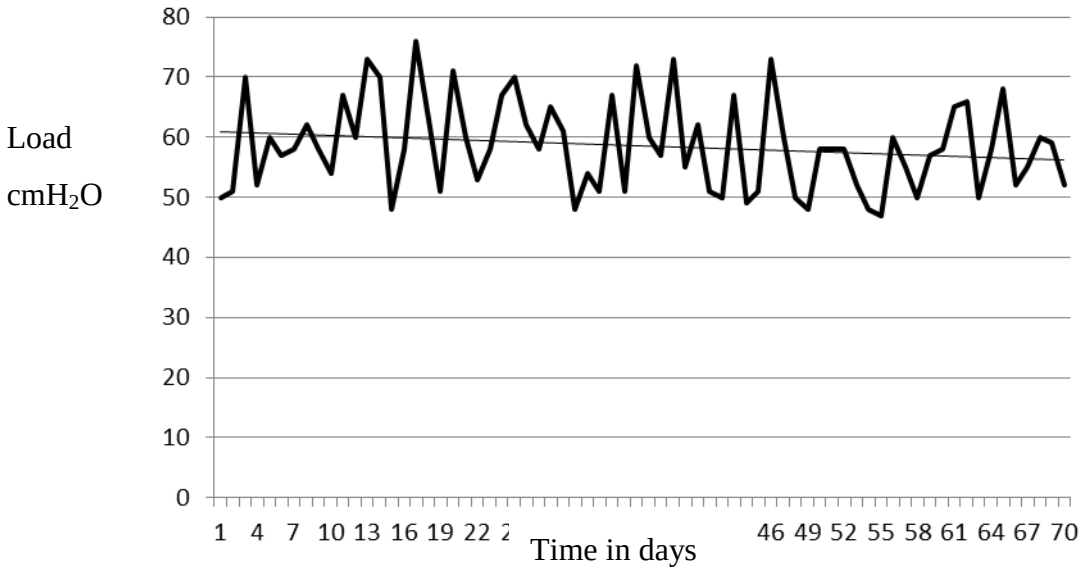
Subject 20 was a 53 year old male who was a non-smoker and lived with his wife and son. His TFC score was 6. UHDRS:TMS 46 and cognitive score 120. Adherence was 99% as recorded by diary and 100% as recorded by the device. The study data show an increase in MIP and PCF and a decrease in SNIP and sit to stand, see Table 65. The resistance provided by the device showed a decrease of approximately 5cmH_2O over the time of the study see Figure 53.

Table 65 Subject 20 study data

	Baseline 1	Baseline 2	Final	Change final – baseline 2
SNIP (cmH_2O)	80	97	93	-4
MIP (cmH_2O)	99	83	90	7
PCF (L/min)	547	527	530	3
Sit-stand		8	7	-1

SNIP Sniff nasal inspiratory pressure (cmH_2O)
MIP Maximal inspiratory pressure (cmH_2O)
PCF Peak cough flow (litres/minute)

Figure 53 Subject 20: Resistance provided by device during training programme



Facilitators, barriers and perceived benefits of the training programme

The following data were collected by the researcher as study notes written during visits. The main facilitator was having a routine for the exercises. On occasion the subject would get breathless, but after a short rest he was able to continue with the training. The subject found that the training was OK and did not interfere with his life. He did not perceive any benefit from the training.

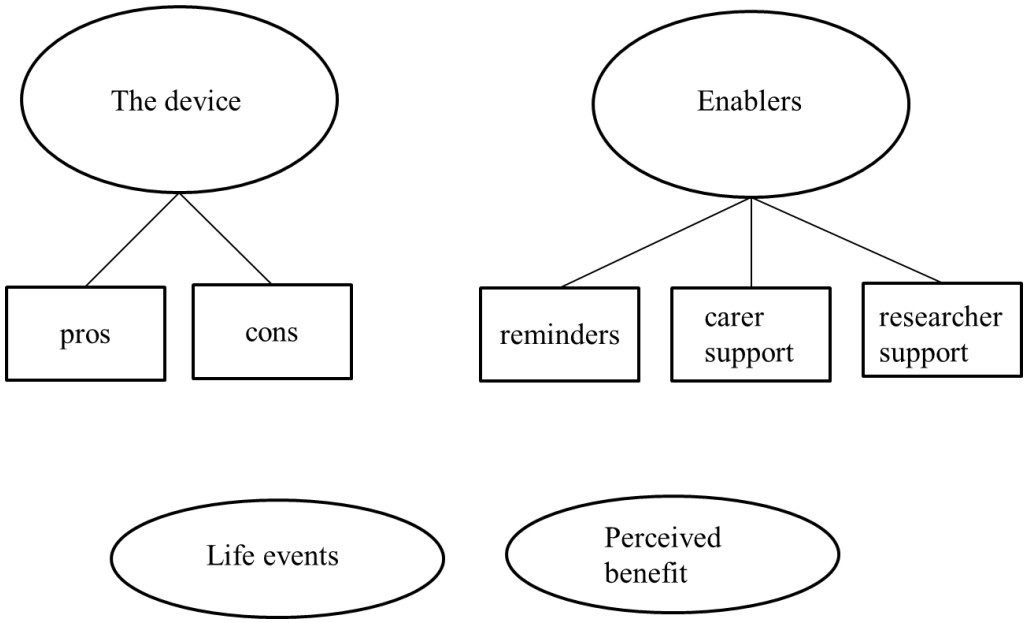
9.4 Adherence to inspiratory muscle training in people with Huntington's disease

Adherence was measured by a diary and by the number of sessions completed on the device. Adherence as measured by the device was similar between groups, 70.67% ±26.35, range 49-100 and 74.53% ±21.03%, range 37-98 for the intervention and sham groups respectively, but was recorded differently in the diary 62.33% ±32.75, range 36-99 and 83.62% ±16.10, range 58.30-100 for intervention and sham groups respectively.

9.4.1 Perceptions of people with Huntington's disease regarding intervention

The perception of participants regarding the intervention was analysed through the responses to interview questions. Five participants from the intervention group and three from the sham group were interviewed by an independent researcher. Audio recordings were transcribed see Appendix 8, coded and themes generated. The codes were: frequency of use; support from carer; support from researcher; ease of use of device; problems with device; reminders; carers responsibility; barriers; the future; facilitators, participation in research. From these codes the major themes of the device and enablers were generated and two sub themes of life events and perceived benefit, see Figure 54.

Figure 54 Themes from interview data



9.4.2 The device

Six interviewees felt that the device was easy to use e.g.

"small easy to use, it doesn't take up any space" (carer, subject01).

Difficulties with the device included the mouthpiece (n=4), the icons (n=1) and the inability to see how many breaths were left (n=2) and the device not working correctly (n=3). Three participants used the device without the mouthpiece and one fashioned a new mouthpiece

"the biggest difficulty we had was with the mouthpiece because with the Huntington's the muscle coordination is quite complicated to get the mouthpiece in and to get [him] to seal around the bit……. it was made a lot easier by cutting the ends of the mouthpiece off" (carer subject 11).

One participant felt that the icons on the buttons were not intuitive

"…why do you need to press the on button to go to the menu button and why the up and down button on the left, why is that a play button?" (subject12)

Problems with the device were

" a couple of times .. the device seemed to jam" (carer subject11);

"there should be fourteen readings on there, there might only be ten or something" (carer subject01);

the device seemed to not work properly" (subject 17);

"he couldn't see how many breaths were left" (carer subject 05);

"the screen goes blank, it doesn't tell him how many breaths you know?" (carer subject 01).

Although there were problems with the device, participants continued with the training once or twice a day.

9.4.3 Enablers

Participants and carers perceived that support from carers and the researcher, plus creating reminder systems enabled them to carry out the exercises. Six of the eight participants interviewed required support from carers in order to carry out the training. Support was needed for cleaning and assembling the device:

"well what I do in the morning is I put the device together with the mouthpiece….and when he's had his breakfast I say "go and do your breathing"" (carer subject01);

"I'm not sure if he would manage to get it on and off himself, I think he would need someone independent to do that, like switching it on and loading it" (carer subject13).

Carers also needed to coach the participants:

"I would stand there and go "in, out" and he'd do it perfectly then. Breathe in, breathe out and he'd know which way he was going. But sometimes he'd get a bit lost in that" (carer subject 05)

Carers also expressed concern over their responsibility:

"it was my fault, I wasn't there, so I wasn't sure what was supposed to be happening" (carer subject 01)

A comment made by subject 11 mother after the recorder was turned off:

"*the parent/child relationship is sometimes difficult, as the onus is on us to remember to do the exercises and there is an element of guilt if we forget."*

Support was provided by the researcher with alternate weekly phone calls and home visits, which were perceived as helpful.

"yes, I mean it helps to go over what's going on and her turning up to remind you" (subject 12)

"they were good, important to see that he was progressing, doing it properly" (care subject 05)

"if I'm having a problem I can say something" (carer subject 01)

"having that extra input was quite helpful" (care subject 11)

Subjects and carers used different systems to act as reminders to carry out the exercises::

"definitely for us the morning is part of a routine" (carer subject 08)

"I kept the device in view otherwise I think I would have forgotten it" (subject 14)

" my wife reminded me" (subject 17)

"having an alarm helped" (subject 12)

"I just knew" " he would remind us" (subject 13, carer subject 13)

9.4.4 Life events

Life events acted as barriers to carrying out the exercises:

"simply to get it done amongst all the other things" (carer subject 11)

"when I went away for a few days I forgot to take it with me" (subject 12)

"he was full of cold" "except for the days when he was in day centre" carer (Subject 05)

"we've been busy with trips and things" (carer subject 08)

9.4.5 Perceived benefit

Four participants who were interviewed did not perceive any benefit from the exercises. Benefits that were noted were:

> *"he seems to be able to walk further… but I think that's because he is well" "his speech is worse if anything" (carer subject 01)*
>
> *"swallowing is a lot better" (subject 13)*
>
> *"he told the nurses that he feels a lot better, going upstairs" (carer subject 05)*

Perceived benefit was also linked to participating in the research project:

> *"helping out in the study I'm always up for that" "if it was part of me getting better its worth doing" (subject 12)*
>
> *"well we like to get involved. He's happy to do any sort of studies that come up then because we have done the breathing with you in the Heath, it seems like a logical follow on….and if it's going to help then anything is worth trying" (carer subject 01)*

The inspiratory muscle training intervention was facilitated primarily by support of carers, the ease of use of the device and setting reminders to carry out the exercises. Barriers were issues regarding the device and life events.

9.5 Group analysis of data from intervention study

Data from completers in the intervention and sham groups were analysed. Firstly, training parameters were analysed to explore whether the intervention group did train differently from the sham group. Data related to inspiratory muscle strength, cough efficacy and the functional task were analysed for differences between the groups.

9.5.1 Training parameters

The training load provided by the device was significantly higher (U= 0.00, p=0.003, [2.89,43.28]) in the intervention group (31.66cmH_2O ±16.33) compared to the sham group (8.57cmH_2O), these findings were confirmed when load was calculated as % of baseline 2 MIP: intervention group (49.00%); sham group (20.93%) (U=0.00, p=0.004, [16.11,40.04]). There was no difference in the number of sessions carried out in each group (U=10.50, p=0.255). This information confirms that the intervention group received a training programme that was different to the sham group.

9.5.2 Inspiratory muscle strength

Descriptive analysis of the changes in SNIP and MIP are displayed in Table 66 and Table 67 respectively. SNIP increased in three participants in the intervention group and four in the sham group; MIP increased in four participants in the intervention group and three in the sham group. Effect size was calculated as $\overline{X}_I - \overline{X}s / s_{pooled,}$ i.e. mean of the intervention group – mean of the sham group/ pooled standard deviation from both groups. Baseline 2 MIP for completers was assessed for differences between the groups, as the values had changed when dropouts were excluded from analysis. There was no difference between groups in baseline 2 MIP for completers, Mann-Whitney U=10, p=0.223. The results show an overall increase in inspiratory muscle strength within both groups, although these were not significant and no difference between the intervention and sham groups. The data indicate that respiratory muscle strength does not change significantly after inspiratory muscle training in people with HD.

Table 66 Group analysis of sniff nasal inspiratory pressure

	Intervention mean ±sd [95% CI]	**Sham mean ±sd [95% CI]**
Baseline SNIP (All starters)	43.67 ±31.87 [10.22,77.11] n=6	45.56 ±17.57 [32.05,59.06] n=9
Baseline SNIP (completers)	47.60 ±33.96 [5.43,89.77] n=5	46.00 ±20.06 [27.44,64.55] n=7
Final SNIP	53.60 ±28.31 [18.44,88.76]	53.00 ±18.17 [36.20,69.80]
Change SNIP	6.00 ±13.78 [-11.12,23.12]	7.00 ±18.58 [-10.19,24.19]
Within group analysis	Z=-0.674 p=0.500	Z=-0.593 p=0.553
Mean between group difference [95% CI]	-1.00 [-22.96,20.96]	
Effect size	0.07	

SNIP Sniff nasal inspiratory pressure (cmH_2O)

Table 67 Group analysis of maximal inspiratory pressure

	Intervention mean ±sd [95% CI]	**Sham mean ±sd [95% CI]**
Baseline MIP (all starters)	57.17 ±25.86 [30.02,84.31] n=6	48.89 ±19.37 [34.00,63.78] n=9
Baseline MIP (completers)	62.80 ±24.46 [32.43,93.17] n=5	46.86 ±15.35 [32.67,61.05] n=7
Final MIP	65.80 ±29.52 [29.14,102.46] n=5	50.57 ±20.76 [31.37, 69.77] n=7
Change MIP	3.00 ±16.87 [-17.94,23.94]	3.71 ±9.32 [-4.91,12.34]
Within group analysis	Z=-0.674 p=0.500	Z=-0.851 p=0.395
Mean difference [95%CI]	-0.71 [-18.52, 16.09]	
Effect size	-0.06	

MIP Maximal inspiratory pressure

9.5.2.1 Peak cough flow

Descriptive analysis of the changes in PCF is displayed in Table 68. PCF increased in three participants in the intervention group and four in the sham group. The results show an overall non-significant increase in PCF in both groups, with no difference between the intervention and sham groups. The data indicate that PCF does not significantly change after inspiratory muscle training in people with HD.

Table 68 Groups analysis of peak cough flow

	Intervention mean ±sd [95% CI]	**Sham mean ±sd [95% CI]**
Baseline PCF (all starters)	407.33 ±138.91 [261.56,553.11] n=6	316.78 ±97.49 [241.84,391.71] n=9
Baseline PCF (completers)	415.80 ±153.57 [225.12, 606.48] n=5	334.00 ±101.64 [240.00,428.00] n=7
Final PCF	448.40 ±144.97 [268.40, 628.40] n=5	370.71 ±89.00 [288.40,453.03] n=7
Change PCF	32.60 ±65.08 [-48.21,113.41]	36.71 ±91.84 [-48.22,121.65]
Within group analysis	Z=-1.095 p=0.273	Z=-0.676 p=0.499
Mean difference [95% CI]	-4.11 [-111.34,103.11]	
Effect size	0.09	

PCF Peak cough flow (litres/minute)

9.5.3 Sit to stand

Descriptive analysis of the changes in the number of sit to stand in 30 seconds is displayed in. Table 69. Sit to stand increased in two people in the intervention group, with no participants showing an increase in the sham group; it remained the same in two participants in the intervention group and three in the sham group. The results show an overall increase in sit to stand in the intervention groups and a decrease in the sham group. The decline in sit to stand in the sham group may have been influenced by one participant who stopped to pull up his trousers during the test and the participant was not able to repeat the test. The data were re-analysed excluding this participant, with the findings remaining largely unchanged, effect size 1.18. The minimal detectable change for SS in HD is 2.2 (Khalil 2012); the mean difference of 1.74 therefore indicates no clinical difference between the groups.

Table 69 Group analysis of sit to stand in 30 seconds

	Intervention mean ±sd [95% CI]	**Sham mean ±sd [95% CI]**
Baseline SS (all starters)	8.00 ±4.05 [3.75, 12.25] n=7	11.78 ±4.63 [8.22, 15.34] n=9
Baseline SS (completers)	8.00 ±4.53 [2.38,13.62] n=5	12.00 ±5.03 [7.35,16.65] n=7
Final SS	8.60 ±4.16 [3.44,13.76] n=5	10.86 ±4.30 [6.88,14.83] n=7
Change SS	0.60 ±1.52 [-1.28,2.48]	-1.14 ±1.46 [-2.50,0.21]
Within group analysis	Z=-0.816 p=0.414	Z=-1.841 p=0.066
Mean difference [95% CI]	1.74 [-0.19,3.68]	
Effect size	1.28	

SS Sit to stand (frequency)

9.6 Summary of intervention study

The intervention study aimed to investigate the feasibility and benefit of inspiratory muscle training as a potential management strategy for people with Huntington's disease. The following null hypotheses were not rejected:

H_{08} People with HD will not adhere to an inspiratory training programme as defined as completing less than 85% of the programme;

H_{09} Inspiratory muscle training does not improve respiratory muscle strength in people with HD;

H_{010} Inspiratory muscle training does not improve peak cough flow in people with HD;

H_{011} Inspiratory muscle training does not improve sit to stand in 30 seconds performance in people with HD.

The data collected from the interviews demonstrated that inspiratory muscle training is feasible for people with HD and that carers and setting a routine facilitated carrying out the exercises. The main barriers were forgetting or being busy with other activities. Problems with the device included comfort of using the flange and the length of time required to charge the device.

10 Intervention study discussion

10.1 Intervention study

The aim of the intervention study was to investigate whether inspiratory muscle training could increase inspiratory muscle strength and thus increase capacity of the respiratory muscle pump. Participants were recruited and allocated to either the intervention group or sham group using the minimisation method of random allocation. The minimisation method was successful in allocating participants to the groups based on confounders of respiratory function i.e. age, gender and smoking habit see Table 51. This method of balancing between groups was used as it is recommended for studies with small numbers as it enables balance between groups for prognostic factors (Altman and Bland 2005). On consideration of all demographic data, differences were noted between the groups, with the intervention group including participants who were functionally and cognitively less able, although statistical analysis demonstrated that the differences were not significant. These factors may have led to more participants dropping out of the intervention group compared to the sham group, see Table 52. The dropouts from the intervention group tended to have weaker inspiratory muscles, lower functional capacity and worse motor function than those who completed the intervention. Lower physical ability is reflected in reasons for withdrawing from the intervention i.e. decreased co-ordination (x3); inability to generate sufficient volume and flow and inability to 'get on' with the training. These reasons differed from those of participants who withdrew from the sham group i.e. inability to learn new a skill and lived alone; other health issues; did not follow protocol and lived alone. Reasons for withdrawal in the sham group therefore tended to be psychosocial rather than the physical reasons in the intervention group highlighting the complexity of HD as a condition. As motor function in terms of UHDRS:TMS and inspiratory muscle strength appeared to influence completion of the study, they could be considered as confounding variables in future studies. Smoking would still be considered a confounder as it is the most important cause of chronic obstructive pulmonary disease worldwide (Mannino and Buist 2007) and as such influences respiratory function. Age and gender could be removed as confounders, if %predicted values are used as outcomes.

Adherence to the intervention measured via the device was 71% and 75% for participants who completed the intervention and sham programmes respectively, with a range of 37-100% across both groups. These figures correspond to partial compliance according to categorisation suggested by Fry et al (2007), but are favourable when using a more conservative cut off point of 50% as suggested by Khalil et al. (2012). Adherence was similar

between groups with one person in each group below the 50% cut off and no significant differences in the number of sessions performed by each group. These adherence values were similar to wheelchair athletes 63-79% (Goosey-Tolfrey et al. 2010) but less than for people with MS which ranged from 81-90% (Chiara et al.2006; Fry et al. 2007; Pfalzer and Fry 2011) and ALS 82-85% (Cheah et al. 2009) and much less than trained athletes 95-97% (Romer et al. 2002b; Volianitis et al. 2001). Adherence may have been reduced due to the current study being home based and therefore unsupervised by the researcher. Supervised studies have shown adherence of 100% (Enright and Unnithan 2011). Decreased adherence in people with HD may also be due to complexity of the condition including apathy which is thought to interfere with functional activities even when the necessary motor and cognitive capacity is retained (Hamilton et al. 2003).

Group analysis of data show no difference between the intervention and sham groups in terms of inspiratory muscle strength (SNIP effect size -0.07, MIP effect size -0.06) and cough efficacy (PCF effect size -0.09) following the six week intervention. Although the functional task of sit to stand had a large effect size, 1.28, the mean difference of 1.74 is less than the minimal detectable change of 2.2 identified by Khalil (2012). The study was underpowered with a post-hoc power calculation of 0.052 (PS software), which could indicate a type II error, with the real effects of IMT in people with HD remaining unknown.

The training programme i.e. 30 breaths, twice a day, seven days/week for six weeks with a resistance of 50% of MIP was based on previous research using the POWERbreathe device (Romer et al. 2002a; Volianitis et al. 2001). The resistance for the sham group was based on evidence from Geddes et al (2008), established in studies on people with COPD and a mean baseline MIP of 42-72cmH_2O. The mean values for MIP in this study are at the lower end of this range; see Table 67, therefore an absolute value for sham resistance may not be applicable. The mean value for resistance in the sham group was 8.57cmH_2O, but this represented a mean of 20.93% of their baseline MIP. The resistance based on %MIP was significantly lower than that of the intervention group (49%), but may still have provided a training effect. This result is similar to the findings in a study in people with COPD, when no differences were found between training at 52%MIP and 22%MIP (Preusser et al. 1994), yet a systematic review concluded that greater increases in MIP are seen with training at higher rather than lower intensities (Geddes et al. 2008). This highlights a need for further research on providing overload to the respiratory muscles in people with different pathological conditions and thus different causes of decreased capacity and increased load on the respiratory pump.

In this study, both intervention and sham groups demonstrated increases in inspiratory muscle strength but these were not statistically or clinically significant compared to the significant increase in MIP of 13cmH_2O in the meta-analysis on people with COPD (Gosselink et al. 2011). Participants in both groups may therefore have experienced a training effect. The effect may have been due to the resistance providing an overload and thus increasing the strength of the inspiratory muscles and/or taking regular deep breaths may have increased lung volumes and altered the biomechanics of the respiratory muscles. Resistance of 50% MIP was provided by the POWERbreathe in the intervention group, based on the initial two breaths of each training session. Theoretically, as strengthening occurs, the resistance increases thus satisfying the principles of progressive overload (Kraemer et al. 2002). This was demonstrated in four participants in the intervention group see Figures 51-54, with increases in training load ranging from approximately 1-10cmH_2O through the training period. Interestingly, subject 20 was the only participant with 100% adherence yet data show a decline in load of approximately 3cmH_2O across the training period and a reduction of 4cmH_2O in SNIP. This participant had the highest SNIP score in the sample, 97cmH_2O, so it is possible that the load of 50%MIP was not sufficient to increase strength. Studies in people with PD (Inzelberg et al. 2005) and MS (Klefbeck and Nedjad 2003) demonstrated significant increases in MIP when training resistance was increased to and then sustained at 60%MIP. The American College of Sports Medicine guidelines recommend a load of 60-70% 1 RM, 1-3 sets of 8-12 repetitions, with 2-3 minutes rest between sets, 2-3 times per week (Kraemer et al. 2002) but few studies in people with neurodegenerative conditions follow all of these recommendations. In the sham group, resistance was set at a constant level and therefore progressive overload would not occur, however constant overload may have occurred as the % MIP ranged from 7-42% baseline MIP.

The non-significant increase in inspiratory muscle strength seen in both groups was similar to that in people with ALS (Cheah et al. 2009) who took part in a similar training protocol. The pathological changes in ALS affecting both peripheral and central nervous systems may mean that strengthening of muscle is harder to achieve and that the changes in strength may be due to biomechanical adjustment as a consequence of regular deep breathing exercises. This may also have been an influencing factor in the current study. Daily deep breathing exercises in people with PD significantly improve FVC (Genç et al. 2012) which will increase the thoracic cavity, and potentially place the diaphragm in an optimal length and shape to increase strength of contraction (De Troyer and Wilson 2009). An increased FVC will also decrease the elastic load on the respiratory system, decreasing the work of breathing (Bach

and Kang 2000) which may influence the efficiency of the respiratory muscles. In people with advanced MS however, IMT significantly increased MIP compared to a control group that included deep breathing exercises (Klefbeck and Nedjad 2003). No details were given regarding the deep breathing exercises, only that it was part of the routine physiotherapy treatment that served as the control arm of the study. The intensity of the exercises therefore may not have been sufficient to alter FVC and consequentially MIP.

The results from group analysis results differ from IMT studies in people with MS (Fry et al. 2007; Klefbeck and Nedjad 2003; Olgiati et al. 1989) and PD (Inzelberg et al. 2005) and studies with similar interventions in untrained healthy people (Downey et al.2007; Edwards et al.2008; Witt et al. 2007). Only two of the above studies in people with ALS and MS had a similar intervention to the current study i.e. participants randomised to either intervention or sham (Cheah et al. 2009; Inzelberg et al. 2005). Other studies had a control group with no intervention (Fry et al. 2007); breathing exercises (Klefbeck and Nedjad 2003) or no control group (Olgiati et al. 1989). All of the above studies used a threshold device, which requires the participant to overcome an initial load therefore, theoretically, strengthening inspiratory muscles at the lung volume at which the resistance is overcome. The POWERbreathe device chosen for this study was a technologically advanced device that provided resistance throughout the breath and therefore potentially strengthening the inspiratory muscles throughout their range of action.

The degree of disability may influence the outcome of IMT studies. The current study included people with early to late stage HD, whereas the studies in PD (Inzelberg et al. 2005) and MS (Fry et al. 2007; Pfalzer and Fry 2011) predominantly included people with mild/moderate disease severity with only one including people with advanced disease (Klefbeck and Nedjad 2003). These studies all showed positive findings irrespective of disease severity, but the co-existence of behavioural and cognitive dysfunction with motor deficits in people with HD may impact on an individual's ability to undertake inspiratory muscle training.

Striatal dysfunction leads to chorea being more dominant in the early stage of the disease followed later by rigidity and bradykinesia (Andre et al. 2010; Han et al. 2010) affecting motor control of the face, mouth and arms which may influence the ability to physically accomplish placing the training device in the mouth. Dysfunctional sensorimotor integration within the basal ganglia (Smith et al. 2000) will lead to inco-ordinated movements that may include volitional aspects of breathing required for inspiratory muscle training. Inspiratory muscle training is a voluntary breathing activity and therefore requires appropriate integration

of cortico-spinal and bulbo-spinal pathways. Although little evidence exists to confirm that this integration occurs (Haouzi 2011), higher cortical involvement must be necessary for the planning and sequencing of breathing pattern in inspiratory muscle training. The co-ordination issues faced by the participants in this study may be due to lack of integration within the striatum leading to motor planning deficits (Giralt et al. 2012; Harrington et al. 2012).

From a healthy person's perspective, breathing in and out of a hand held device is a relatively straightforward task, but this did not appear to apply to people with HD. During the study the researcher had to break down the task into component parts, give slow, brief instructions and use visual cues to enable the participants to carry out the technique correctly. Traditionally the basal ganglia was thought to be just involved in the control of motor function, it is now considered to be essential in the learning of new complex movements which include emotional, motivational and cognitive components (Haber and Calzavara 2009). This may help explain the increased anxiety levels, 'not getting on' with the training programme and inability to learn a new skill in those who dropped out of the study. For those that remained in the study, the habituation period of one week may have been insufficient, or more home visits may have been necessary in that week to ensure the programme was being carried out correctly. This lengthened learning time may have influenced the efficacy of the intervention.

The controversy surrounding efficacy of inspiratory muscle training may be extended when abnormalities within skeletal muscle in people with HD is included. Proponents provide statistical evidence that inspiratory muscle training improves exercise limitation (Ambrosino 2011; McConnell 2012), whilst opponents question whether respiratory muscles can in fact be trained (Patel et al. 2012) and attribute positive findings to better performance of the outcome measure due to the manoeuvre being similar to the intervention (Polkey and Moxham 2004). The controversy behind the ability to train respiratory muscles is based on people with COPD, in whom the diaphragm is at a biomechanical disadvantage due to hyperinflation (Patel et al 2012). This would not be the case in people with HD, as the converse is true i.e. the lungs are underinflated as demonstrated by decreased FVC. However, abnormalities in mitochondrial function which are thought to lead to muscle atrophy (Ciammola et al. 2011) in people with HD may influence the ability of the muscle to be strengthened. Ciammola et al (2011) suggest that low anaerobic threshold levels and elevated blood lactate levels in people with HD are attributable to abnormal oxygen utilisation. The question that is yet to be answered is whether skeletal muscle in people with HD can be strengthened despite muscular cellular dysfunction.

The decreased inspiratory muscle strength observed in this study may not be solely attributable to underlying HD pathology; general de-conditioning may play a role. Deconditioning due to disuse or inactivity will cause decreased muscle strength (Bortz 2005) which is related to respiratory muscle strength (Buchman et al. 2008). Evidence for effectiveness of inspiratory muscle training in people who are healthy but untrained is strong (Downey et al.2007; Edwards et al.2008; Kellerman et al. 2000;Suzuki et al 1993; Witt et al. 2007) and would suggest that if decreased strength is due to de-conditioning, this could be reversible. The potential for strengthening inspiratory muscles in people with HD who have decreased activity levels and are de-conditioned is therefore possible.

The intervention study included outcome measures related to function pertinent to people with HD. Cough efficacy decreases linearly with measures of disease severity and is an influencing factor in predisposition to type 1 respiratory failure. Strengthening of the inspiratory muscles would lead to increased inspiratory capacity, this increased volume optimising the length tension relationship of the expiratory muscles resulting in greater expiratory flow (McCool 2006a). Group analysis of the data demonstrate that PCF, in a similar pattern to SNIP and MIP, increased non-significantly within groups but the effect size of 0.09 indicated no difference between the groups. Although IMT studies in people with neurodegenerative conditions did not assess cough efficacy, EMT studies in people with MS (Gosselink et al. 2000) and PD (Pitts et al. 2009) did show improvements in subjective and objective cough measures. EMT appears to be a more logical approach to increasing cough efficacy, but limited evidence and lack of suitable equipment meant that it was not chosen as an intervention in this study.

This study was concerned not only with physiological consequences of inspiratory muscle training, but in line with recommendations (Polkey et al. 2011) an outcome related to function was included. The 30 second sit to stand is a functional measure of an activity of daily living that incorporates elements such as lower body strength and co-ordination (Macfarlane et al. 2006). The findings demonstrated a different pattern to SNIP, MIP and PCF, in that the sham group decreased in the number of sits to stands in 30 seconds, and the intervention group increased with an effect size of 1.28 see Table 69. When the irregular measurement of one participant was removed the findings remained relatively unchanged, effect size 1.18. This is considered a large effect size (Cohen 1988), however the mean difference (1.74) was less than minimal clinical difference of 2.2 for this outcome measure in people with HD (Khalil 2012). An outcome measure of sit to stand ability in terms of time

taken to complete a set number of manoeuvres rather than the number of manoeuvres in a set time may provide more sensitive data to measure functional activity.

It is unclear why the sham group should decrease in the number of sit to stand manoeuvres relative to the intervention group, when no significant difference was found in inspiratory muscle strength. Analysis of individual participants indicated that one person in the sham group increased sit to stand, three decreased and three remained the same. One person completed 21 manoeuvres at baseline and 19 on the final assessment. These values were much larger than those reported for healthy older males, 14.2 (Rikli and Jones 1999) and therefore the decrease on second assessment may be due to regression to the mean. With the small sample size this reading will have a large influence on the group analysis.

Similar results were found following an inspiratory muscle training in people with MS, yet a significant improvement was demonstrated in balance and a non-significant improvement in six minute walk distance were found (Pfalzer and Fry 2011). These improvements were greater in those people with mild disability. The functional changes were attributed to the postural role of the respiratory muscles. The diaphragm acts as a stabiliser during upper limb movements with the intercostal and parasternal muscles involved in trunk rotation (Hudson et al. 2011) with the relationship between postural control and respiration being dependent upon the body's movement and needs (Massery et al. 2013). The lack of improvement in sit to stand, both in Pfalzer and Fry (2011) and the current study may be due to the outcome measure being dependent more on lower limb strength than on postural stability and balance.

Review of the study notes and interviews revealed that only one participant in the intervention group perceived benefit from inspiratory muscle training, the improvement being increased ability to climb stairs. This participant demonstrated an increase in load of approximately 10cmH_2O during the training and increased SNIP of 7cmH_2O, but no change in sit to stand. It is possible that the improvement in climbing stairs was due to improved postural mechanics, or was unrelated to the intervention.

Inspiratory muscle training is thought to attenuate the proposed reflex decrease in blood flow to peripheral muscles consequentially respiratory fatigue occurs, by reducing the energy requirements of the respiratory muscles (Turner et al. 2012). This attenuation would enhance performance of physical activity that is halted due to peripheral muscle fatigue. In this study the lack of improvement in the functional task suggests that fatigue of the respiratory muscles did not influence task performance. This may be due to either the task being not sufficiently arduous and/or the respiratory muscles did not fatigue. The study by Inzelberg et al. (2005) in people with PD did not measure a functional task, but observed a decrease in perception of

dyspnoea following an intervention similar to this study. This may indicate an increase in capacity of the respiratory system to withstand an increased load and therefore reduces the physiological element in the perception of dyspnoea. Evidence for improvements in dyspnoea are strong in people with COPD and accompanies an increase in exercise capacity and quality of life (Geddes et al. 2008; Gosselink et al. 2011), but is weaker in healthy untrained subjects (Downey et al. 2007).

Functional benefits perceived by the participants were improved swallow, n=2 and improved speech, n=1. These three participants were all in the sham group, the improvements possibly due to regular breathing exercises rather than respiratory muscle training. Breathing exercises are encouraged in the early stages of HD in order to improve speech (Hamilton et al. 2012), which highlights not only the highly integrated functions of swallow and breathing (Davenport et al. 2011) but also speech (Aleksandrova and Breslav 2009). The effect of breathing in a regular pattern, as required for the sham intervention, may provide sensory and motor feedback to and potentially alter the central pattern generator of breathing. If the IMT intervention improved the regularity of breathing pattern this may provide benefit to the integrated functions of speech and swallow. This is a hypothetical proposition as the exact mechanisms of integration of these functions are not yet fully understood (Feldman et al. 2013).

This study showed no changes in inspiratory muscle strength, cough effectiveness or a functional task following inspiratory muscle training. This may be due to the non-specificity of the training protocol i.e. resistance against 50% MIP. For people with neurodegenerative conditions improvements in cough, exercise tolerance and physical activity may be functional goals and therefore training protocols may need to be adapted for these specific outcomes. In order to improve cough effectiveness, a power based protocol with lighter loads and faster inspirations may be appropriate. Conversely a protocol similar to the test of incremental respiratory endurance (Chatham et al 1999) may be more appropriate for improving physical activity outcomes. It is also possible that a longer intervention time is required for people with neurodegenerative conditions compared to healthy subjects in order for strength training against a background of neural dysfunction to show changes in muscle strength.

Two major themes and two sub themes emerged from structured interviews with five participants from the intervention group and three participants from the sham group regarding participants' perceptions of inspiratory muscle training. The major themes were the device

and enablers, with sub themes of life events and perceived benefit. As the interviews were structured around a number of set questions, a narrow breadth of data were gathered. Support from carers was a strong component of the enablers theme, with carers being involved in assembly, set up, cleaning of the device as well as coaching participants through the training. This theme was similar to that found by Khalil et al. (2012) who found that commitment of the caregiver was key to the success of an exercise intervention in people with HD and suggested that physiotherapists should work with caregivers to assist them in their supporting role. Wright et al (2013) found that carers of people with HD play an active role in deciding if the person with HD should participate in a study and then facilitate attendance at appointments and data collection throughout the study. By contrast, the participant with HD tended to play a passive role with a focus on physical and behavioural changes during the trial. Four participants in the current study lived alone, only one of whom completed the study, which may be related to the active role played by caregivers in intervention studies.

Two carers in the current study expressed feelings of responsibility, one of blame (carer subject01) and one of guilt (mother subject11). The feeling of blame was that the carer had not been present for the initial information giving meeting and that this meant she was not sure how the device worked or the details of the protocol. This feeling confirms the suggestion from Khalil et al (2012) that therapists, and in this context, researchers, should assist caregivers in the supportive role. The feeling of guilt was related to the burden placed upon the carer to remember to do the exercises and as a parent of the participant they felt that the onus was on them to remember rather than the participant. Wright et al. (2010) suggest that further research is needed to understand the burden and role of carers in HD research in order to enhance their experience and also improve recruitment and retention in studies.

Khalil et al (2012) attribute adherence to an exercise intervention to both caregiver involvement and researcher support. In the current study, weekly support provided by the researcher was perceived as helpful by participants and carers, both in terms of a reminder to carry out the exercises and as a trouble shooter. The role of the researcher as trouble shooter was appreciated by participants and carers as a number of issues arose concerning the training device. Although most interviewees felt that the device was easy to use in general terms, four had problems with the mouthpiece whilst others had problems with the device working correctly. Supported by the researcher, participants adjusted the device to suit their own needs, either by fashioning a new mouthpiece or removing it completely. Although there are no inherent dental features to HD pathology (Manley et al. 2012), the issues with oral

compatibility of the device are more likely to relate to muscle incoordination and inability to keep a seal around the mouthpiece. This has been recognised in a number of neurodegenerative conditions in relation to measurement of respiratory function (Uldry and Fitting 1995).

Some participants took an active role in remembering to carry out the exercises such as leaving the device in view, setting an alarm and getting into a routine. This suggests that these participants potentially had insight into cognitive (Peavy et al. 2010), particularly memory loss (Paulsen et al. 2008) and behavioural e.g. apathy, lack of initiative, elements of HD and set up strategies to overcome these in order to enable them to carry out the exercises. Particular negative issues with the device included jamming, the screen not showing the number of breaths yet to complete and length of charging time. As this was a home based study, the researcher was unable to give advice on inability to see the numbers of breaths left, as the source of the problem was unknown. For some participants, study notes provided information relating to incorrect use of the device, in that the button to start the exercises had not been pressed. It remains unclear as to why the screen went blank during the exercise, but could possibly be due to the charge level of the device. One participant expressed surprise at the length of time required for charging and this information was then used to encourage subsequent participants to charge the device overnight.

Life events often acted as a barrier to carrying out the exercises with activities such as being at a day centre (subject05) or on trips (subject08) meaning that training was not performed. Trying to fit the training in around other things (subject11) may create an extra burden for participants.

Four participants did not perceive any benefit from the training, although one did feel that speech was better (subject13) and one that walking upstairs was better (carer subject05). The potential of some benefit to the individual by taking part in a research study was highlighted by a carer and a participant. The carer of subject 01 and subject12 expressed their desire to get involved in research in terms of being happy to do any research related to HD, but qualified this with comments about getting better. This altruism is therefore not ‘pure’ but context dependent and related to helping future patients including their own family as described by Hallowell et al. (2010). Hamilton et al. (2010) also discuss the risk benefit of involvement in research and as IMT is a low risk intervention this may have encouraged participation in the context of developing therapy for a genetic condition.

10.2 Conclusions from intervention study

This is the first study investigating an intervention for respiratory dysfunction in people with HD, which may reflect the current approach to respiratory problems in this population. The intervention study was underpowered and therefore it is not known whether IMT may increase capacity of the inspiratory muscles in people with HD. Both groups demonstrated increases in inspiratory muscle strength and cough efficacy, but these were not significant and may be due to undertaking regular deep breathing exercises rather than as a consequence of resistance training. Alternatively, due to low measures of respiratory muscle strength in the sample, the resistance offered to the sham group may actually have provided a training load. Participants did adhere to the training protocol, and perceived that carer support, ease of use of the device and the setting of reminder systems enabled them to carry out the exercises. Management of respiratory problems in people with HD has been described as restorative at the later stages of the disease (Busse et al. 2008) rather than preventative. This was reflected and developed upon in the European Huntington's disease network physiotherapy guidance document (EHDN Physiotherapy working group 2009) with specific commentary that respiratory problems may arise at any stage of the disease. The work within this thesis has helped to establish respiratory dysfunction within a treatment based approach to management of people with HD (Quinn and Busse 2012). The results of this study may therefore lead to investigation of other interventions for the management of respiratory problems in people with HD such as maximal insufflation-exsufflation and non-invasive ventilation as discussed in section 7.4.

11 Thesis conclusions

11.1 Synthesis of findings from the observation and intervention studies

This thesis was based on two studies that sought to generate knowledge regarding respiratory function in people with Huntington's disease. The underlying clinical issue was that people with HD die from respiratory failure, yet there was no quantification of respiratory function or exploration of factors that may influence respiratory function in people with HD. In relation to the MRC framework for complex interventions (Craig et al. 2008), these studies provide an evidence base and have generated knowledge that can develop theory regarding respiratory function and potential management of respiratory problems in people with HD. The observation study established that respiratory function is decreased in people with manifest HD compared to those who are pre-manifest and healthy control subjects and that this decline is linearly associated with disease progression as measured by motor symptoms and functional activity. Of particular clinical relevance is that cough becomes ineffective at the middle stage of the disease and therefore regular monitoring of peak cough flow is essential for the prevention of aspiration pneumonia. The intervention study developed from preliminary analysis of data from the observation study as it was clear that there were physiotherapy interventions that could be instituted to manage the problems of decreased ventilatory capacity, decreased respiratory muscle strength and decreased cough efficacy leading to retention of secretions. A systematic review of the literature indicated that inspiratory muscle training was one such intervention and therefore the feasibility and benefit of IMT were assessed in people with HD. Although physiological benefit was not determined in the small sample, the findings suggest that the training is feasible. The key clinical implications of this study are that respiratory function should be regularly monitored in people with HD and that problems should be managed based on strategies that have sound physiological rationale and potential benefit. Dissemination of clinical case study findings will help develop appropriate strategies for people with complex motor, cognitive and behavioural problems.

From a theoretical perspective, a model of respiratory failure in people with HD was developed from existing evidence and postulation from that evidence. The underlying conceptual framework was developed from the categorisation described by Hart (2008) i.e. type 1 hypoxaemic respiratory failure is lung failure whilst type 2 hypercapnic failure is respiratory pump failure due to an imbalance between central neural drive, capacity of the respiratory muscle pump and the load placed upon the pump. Although the predominant

cause of death was known to be aspiration pneumonia which would be a categorised as type 1 hypoxaemic respiratory failure, it was not known if this actually constituted an acute or chronic episode indicating an underlying imbalance between drive, capacity and load with an acute aspiration infection tipping the balance into respiratory failure. The categorisation allowed components of each type of respiratory failure to be explored in depth with the conclusion that people with HD are susceptible to type 1 hypoxaemic respiratory failure and predisposed to type 2 hypercapnic respiratory failure. The linear decline in respiratory function across progression of the disease would suggest that this is not a dichotomous classification but that decreasing ventilatory capacity and subsequent hypoxaemia leads to increasing elastic load driving the respiratory system toward type 2 hypercapnic respiratory failure. The concomitant decline in respiratory muscle strength and increase in resistive load due to upper airway dysfunction provides evidence that people with HD are predisposed to type 2 respiratory failure. Signs and symptoms of respiratory system dysfunction may not be apparent in people with HD as their decreased exercise capacity and physical activity may mask breathlessness on exertion. The complex interrelationships between exercise capacity, physical activity, posture and respiratory function found in this study mean that causal relationships cannot be made.

The underlying cause of respiratory dysfunction in people with HD is still unknown and the framework of respiratory failure can be used to explore theoretical postulation. Type 1 hypoxaemic respiratory failure may be due to swallow dysfunction which is evident in people with HD (Heemskerk and Roos 2011; Kagel and Leopold 1992) and ineffective cough. These two factors indicate that central processing of swallow is dysfunctional and that respiratory muscle strength is inadequate respectively. Central processing dysfunction may indicate that central drive to the respiratory muscles is also impaired as integration between breathing and swallow is known (Bianchi and Gestreau 2009; Butler 2007; Davenport et al. 2011; Hardemark Cedborg et al. 2009). Central drive of the respiratory muscle pump may impact on type 1 hypoxaemic respiratory failure in terms of both aspiration and ineffective clearance of secretions, but may also impact on the balance between drive, capacity and load influencing type 2 hypercapnic respiratory failure. Emerging evidence of brainstem pathology in people with HD (Herndon et al. 2009; Hobbs et al 2010;Rub et al 2014) and evidence of irregular airflow patterns in people with manifest HD in this study support a theory of central respiratory control dysfunction in people with HD . Ineffective cough is likely due to decreased inspiratory and expiratory muscle strength as identified in the observation study. Although there was no improvement in peak cough flow following

inspiratory muscle training in the intervention study, this is to be expected as inspiratory muscle strength also did not increase. The lack of benefit identified in the intervention study poses a number of potential theories. It may be that the model of respiratory failure proposed is not complete, as it would have been presumed that inspiratory muscle training, for which there is evidence of increased diaphragm thickness in healthy people (Enright et al. 2006b) and increased respiratory muscle strength in people with COPD (Geddes et al 2008; Gosselink et al 2011), would increase capacity of the respiratory muscle pump and increase cough effectiveness. More likely reasons for the lack of benefit include the small number of participants, lack of supervision influencing the quality of the intervention and inappropriate sham condition, but further exploration of muscle control needs to be undertaken.

The key motor dysfunctions in people with HD are chorea, dystonia, rigidity and bradykinesia as a result of loss of neurones within the striatum (Estrada Sánchez et al. 2008; Fenney et al. 2008; Reiner et al 2013) which alongside skeletal muscle dysfunction (She et al. 2011) may impact on the generation of muscle force in both normal breathing and during respiratory muscle training. Striatal dysfunction also impairs cognitive planning of motor activity which may decrease the effect of the training programme. Taking these factors into consideration, a longer, more supervised trial is needed to further explore the effect of inspiratory muscle training in people with HD.

The model developed from the conceptual framework provides evidence of respiratory dysfunction in people with HD that needs to be tested in further studies. This study was limited by not assessing central drive and therefore studies incorporating plethysmography, arterial blood gas analysis and airflow-time analysis will develop theories of brainstem involvement in people with HD which could be furthered through animal and post mortem studies. Animal studies could also explore physiological properties of the respiratory muscles and force generating influencing factors. The complex relationships between respiratory function, physical activity and exercise capacity need larger studies with regression analysis and appropriate evaluation of exercise intervention studies to gain a deeper understand of these relationships.

11.2 Limitations of the study

This study is not without limitations; recruitment, outcome measures and adherence to the inspiratory muscle training programme are specifically discussed.

HD as a progressive neurodegenerative condition is relatively uncommon, with a prevalence of 12.3/100,000 in the UK (Evans et al. 2013) and the number of potential participants in a

single site study will always be low. Approximately 170 patients attend the Cardiff Huntington's disease research clinics, with the 67 participants in the observational study being 39.4% of this population. The findings of this study are therefore representative of the South Wales community, but not necessarily of the UK, European or world community as the number of participants is too low to make statistical inference. The findings from this study could however influence larger scale studies such as the European Huntington's Disease Network observational study 'Registry'. The key outcomes of decreased capacity and cough efficacy could be included in this larger study to further understanding of respiratory function in people with HD.

Although the target recruitment for the inspiratory muscle training study was reached, 5 participants (25%) did not continue from the practice week into the intervention stage of the study. Reasons for drop out were related to decreased co-ordination, inability to generate sufficient volume and flow and inability to learn a new skill with the need for carer support as an emergent theme from the interviews. This would suggest that recruitment for further exercise intervention studies should include disease severity as a confounding variable and possibly carer support as an inclusion criterion. These amendments may reduce external validity, but may ensure adherence and completion of adequately powered studies.

All outcome measures had evidence of reliability and validity, except digital analysis of posture, therefore the researcher carried out a reliability study prior to the main study to ensure consistent measurements (Jones et al. 2011). The study is limited by having a non-blinded assessor who was aware of the hypotheses of the study although this had limited impact for the observational study. Some data from healthy participants were collected by MSc students, but consistency was ensured through training and monitoring by the researcher.

Some difficulties were noted during respiratory function tests, in that participants had difficulty in co-ordinating the breathing pattern necessary for the individual tests and that an adequate seal around the mouthpiece sometimes did not occur. Valid measurements were assured by asking participants to repeat the tests until a manoeuvre was deemed acceptable by the assessor i.e. stable reading over three manoeuvres. As the respiratory function tests were all volitional, the amount of effort conferred by the participant influences the maximal values attained. Although enthusiastic coaching is recommended during testing (Miller et al. 2005), it was thought that too many instructions to the participant may result in confusion. As cognition is influenced by HD pathology (Kingma et al. 2008) the techniques were visually

demonstrated, and verbal commands limited to short statements in order to maximise understanding.

The study is limited in the breadth of respiratory variables that were measured; in particular, no measurements were made relating to central drive of respiration. In the planning of the study it was recognised that a large number of variables could be measured and due to experience of the researcher and availability of suitable equipment, measures of mouth occlusion pressure and end-tidal CO_2 were not taken. These measures would provide further data regarding the existence and potential progression of type 2 hypercapnic respiratory failure in people with HD. This study identified abnormalities in breathing pattern via visual analysis of flow volume loops, but further data could be gathered using respiratory inductance plethysmography. This would enable further analysis of the quality and synchrony of movement of the rib cage and abdomen in order to gain understanding of the biomechanics of breathing in people with HD.

Measurement of physical activity was limited to using the IPAQ questionnaire which may not reflect true activity as it relies on memory and cognition, both influenced by HD pathology (Kingma et al. 2008; Paulsen et al. 2008). More accurate assessment of physical activity could be analysed using accelerometers, although these are also limited as they do not give an indication of the type of activity being carried out. A combination of questionnaires, accelerometers and diaries may enhance the validity of measurement of physical activity.

The outcome measures in the intervention study were limited to assess specific hypotheses developed during the PhD study. The hypotheses were based on preliminary findings of decreased muscle strength and limited cough efficacy. Analysis later in the study demonstrated lung volume as a key variable that declines with disease progression and relates to exercise capacity and physical activity. The intervention study was limited in that FVC was not measured and therefore it is not known whether carrying out regular breathing exercises alters lung volumes, as is suggested by evidence in people with PD (Genç et al. 2012).

A strength of the intervention study was that the burden placed upon the participants was minimised by having a home based exercise programme, however this in turn may reduce adherence due to lack of supervision. The weekly contact from the researcher was perceived as a reminder for some participants, but adherence may have been enhanced by further contact. This could be explored in terms of digital reminders e.g. text messages which would be more appropriate than home visits for a study covering a large geographical area. For

some participants, more visits in the practice week may have enabled them to better learn the breathing manoeuvre and to deal with any problems related to the device, which may have improved the number of participants progressing to the intervention stage.

11.3 Clinical implications

This study aimed to investigate respiratory function and explore the feasibility and benefit of inspiratory muscle training in people with HD. The findings from this study provide new knowledge that respiratory function decreases linearly with disease severity, which can be incorporated into clinical guidelines for the management of people with HD and provide a basis for further research.

This study provides the first objective measure of respiratory function in people with HD from pre-manifest to late stage of the disease. The findings show that respiratory function is decreased in people with manifest HD compared to people with pre-manifest HD and healthy control participants and that there is no difference between people with pre-manifest HD and healthy control participants. Relational analysis with measures of disease progression demonstrated a linear relationship between respiratory function and TFC and UHDRS:TMS. This information contributed to clinical guidance for the management of respiratory function and associated factors of swallow and exercise capacity.

Linear regression of PCF and TFC data demonstrate that cough may be ineffective at the middle stage of HD and suggests that monitoring of PCF should in fact be integrated into clinical management of people with HD. If PCF <160L/min, referral to a physiotherapist may be appropriate. Apppropriate interventions could include maximal insufflation/exsufflation (Chatwin et al. 2003) or expiratory muscle training (Gosselink et al. 2000). For patients with PCF >160L/min but <270L/min, regular monitoring and assessment to determine causes of decreased PCF will enable planning of appropriate interventions to maintain adequate cough efficacy as suggested by Bott et al. (2009).

Associated with reduced PCF, swallow capacity was also found to be reduced in people with HD. Swallow capacity can be assessed using a simple timed swallow test. If signs and symptoms of swallow dysfunction are reported, swallow capacity can be assessed and referral made to a speech and language therapist. If swallow dysfunction is suspected, but there have been no obvious signs of aspiration e.g. cough, a chest X-ray can provide information regarding silent aspirations in terms of identifying the lobe affected.

In this study significant relationships between both inspiratory muscle strength and lung volume and exercise capacity and physical activity were identified. The relationships appear

to be complex, and evidence from the literature review shows inconclusive evidence of the influence of exercise on respiratory function in people with neurodegenerative conditions. When considering exercise prescription, the complex relationship between respiratory function, physical inactivity, morbidity and mortality (Buchman et al. 2008b; Jakes et al. 2002) imply that monitoring of respiratory muscle strength is also important

11.4 Recommendations for future work

11.4.1 Focusing and extending the observational study

The observational study could be focused and extended in a number of ways. The number of outcomes measures could be reduced to specifically measure respiratory function, the key outcomes being FVC in terms of elastic load, $FEV_1$and PEFR in terms of resistive load, SNIP and MEP as measures of respiratory pump capacity and PCF as a measure of cough efficacy. This type of data could be collected through the European Huntington's Disease Network Registry study, which would then allow the study to become longitudinal. A longitudinal study would provide more data regarding the rate of decline of respiratory function in people with HD.

The observational study could also be extended by investigating measures of central respiratory drive in people with HD and exploring histologically the role of mutant Huntingtin in breathing control. Future work could include analysis of respiratory pattern using plethysmography and assessment of flow time indices to measure ratio of inspiratory time to total breath time. This would potentially provide information regarding the synchrony of inspiratory drive and whether the respiratory muscles are choreic or bradykinetic. Intensity of respiratory drive could be analysed using mouth occlusion pressure, but inspiratory muscle strength would be a confounding variable. The respiratory system's capability of responding to hypoxaemia, hypercapnia and mechanical loads could be analysed using breath by breath gas analysis in controlled settings. Further use of breath by breath analysis of O_2 and CO_2 at rest would provide further physiological data regarding the existence and potential progression of type 2 hypercapnic respiratory failure in people with HD.

11.4.2 Extending the intervention study

The intervention study was limited by the number of participants completing the study and the relatively few outcome measures used. The aim of the study was to investigate a method of increasing the capacity of the respiratory pump in people with HD and this aim has yet to be realised. Further studies should use protocols that are directly related to the primary

outcome measure e.g. a power based protocol to improve cough efficacy or endurance based protocol to improve physical activity. A number of potential interventions were identified in the literature review e.g. maximal insufflation exsufflation and non-invasive ventilation and further intervention studies could assess their efficacy in people with HD.

The same protocol could be repeated in a larger group, with altered inclusion/exclusion criteria to recruit people with early to mid-stage disease. Outcome measures could include a functional task that is less reliant on lower limb strength, but related more to postural stability e.g. a walk test. Further exploration is required to determine an appropriate sham resistance for people with low inspiratory muscle strength, which would be a percentage of MIP rather than an absolute value.

For those people with PCF <160L/min, the feasibility and benefit of mechanical insufflation-exsufflation could be explored. For those with 160<PCF<270L/min, comparative studies of deep breathing exercises, breathing exercises using incentive spirometry and expiratory muscle training could provide information regarding appropriate methods to improve cough efficacy.

11.4.3 Enhancing validity of measurements in people with HD

The limitations of the study highlighted cognition and poor seal around mouthpieces as issues influencing data collection. Further work could explore the most effective way of collecting respiratory function data from people with HD. This could include actual methods and instructional advice. Methods of measuring lung function and respiratory muscle strength via face mask rather than mouthpiece may reduce the co-ordination and adequate seal needed for the mouthpiece. This would require appropriate validity and reliability studies in people with HD. Methods of learning skills could be explored in people with HD. Studies comparing verbal, visual and potentially digital instructions given to people with HD would provide information on the most appropriate way to teach a person with HD how to carry out an assessment task, but also has implications for intervention studies, like inspiratory muscle training that introduce new skills to the participant.

11.4.4 Exploration of the relationship between respiratory function, exercise capacity and physical activity

Further work needs to be carried out which explores the relationship between respiratory function, exercise capacity and physical activity in people with HD and potentially people with other neurodegenerative conditions. This is a complex relationship which spans all three

domains of the WHO International Classification of functioning, disability and health i.e. impairment, activity and participation.

A longitudinal study measuring respiratory function, exercise capacity and physical activity may provide further information regarding the casual factor in the decline of all three variables. An intervention study with a number of arms e.g. inspiratory muscle training, exercise and control measuring both exercise tolerance and respiratory function may help to explore cause and effect relationships. An intervention study with participation as its focus and outcome measures of respiratory function, exercise capacity and quality of life would help to explore the complex interactions between impairment, activity and participation.

A study of this type could also provide information regarding the influence of physical activity on disease progression, activities of daily living, and cognitive and behavioural factors in people with neurodegenerative conditions.

12 Conclusions

12.1 Conclusions

This study explored respiratory function in people with HD using a conceptual framework of respiratory failure and investigated whether a targeted intervention was feasible and could improve respiratory function in people with HD. The framework provided a structure to explore type 1 hypoxaemic and type 2 hypercapnic respiratory failure in the context of people with HD. The findings demonstrate that people with HD are susceptible to type 1 hypoxaemic respiratory failure due to impaired swallow capacity and cough efficacy. The decreased lung volume, declining linearly with disease progression, may indicate progressive atelectasis leading to type 2 hypercapnic respiratory. People with HD are predisposed to type 2 respiratory failure as a consequence of increased elastic and resistive load and decreased capacity of the respiratory muscle pump. The intervention of inspiratory muscle training to potentially increase respiratory muscle capacity was feasible and did not demonstrate change in respiratory function, cough efficacy or a functional task. Data from interviews with participants suggest that carer support enabled them to complete the study and life events as a barrier to carrying out the exercises.

The data from the observational study identified that respiratory function is decreased in people with manifest HD compared to people with pre-manifest HD and healthy control participants, and that respiratory function declines linearly with disease progression. This is new information which can be integrated into clinical care through regular monitoring of respiratory function. Of specific clinical concern is PCF, which is impaired in the middle stage of the disease and has a significant relationship with swallow capacity. These findings highlight that people with HD are susceptible to aspiration pneumonia from the middle stage of the disease. The relationship between swallow and breathing provides insight into the integration of these functions within the brainstem which may be directly influenced by HD pathology. Respiratory muscle capacity is reduced in people with manifest HD and the situation is made more complex by the significant relationships between respiratory muscle strength, exercise capacity and physical activity. Decreased respiratory muscle strength may be influenced by abnormal neural drive, muscle atrophy and/or deconditioning. The causal factors within these relationships are unknown and additional research is required to gain further understanding. The findings from the observational study were synthesised to produce a model of respiratory function in people with HD which was used as a basis for the intervention study.

In the context of the development stage of the MRC framework for the development and evaluation of complex interventions, the intervention study identified that inspiratory muscle training is feasible in people with HD and that no benefit in terms of inspiratory muscle strength, cough efficacy or functional activity was found. Both groups demonstrated increases in respiratory muscle strength and cough efficacy, but these were not significant and may be due to undertaking regular deep breathing exercises which would decrease elastic load rather than as a consequence of resistance training. Alternatively, due to low measures of respiratory muscle strength, the resistance offered to the sham group may actually have provided a training load. Participants did adhere to the training protocol, although this may have been enhanced by further support from the researcher.

This study is the first to demonstrate that people with HD have decreased respiratory function which makes them susceptible to type 1 hypoxaemic respiratory failure and predisposed to type 2 hypercapnic respiratory failure. These findings therefore have important implications for the therapeutic management of people with HD, particularly in the middle stage of the disease progression.

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14 Appendices

14.1 Appendix 1 Reliability of digital analysis of posture

14.1.1 Overview

The reliability aimed to address the following objective:

- To investigate the reliability of objectively measuring posture in people with Huntington's disease using digital images processed by a bespoke software programme.

The relevant research question was:

- Is digital analysis using a bespoke software programme reliable in measuring posture in people with HD.

The relevant null hypothesis was:

- Digital analysis of posture using a bespoke software programme is not reliable in measuring posture in people with HD as identified by an intra-class correlation of less than 0.75.

Two reliability studies were carried out: one with healthy subjects before the main study commenced and one with people with HD which was analysed before the main data were analysed. Intra-tester within day reliability was carried out with both sets of data.
A decision on the reliability of the measuring tool was based on data analysis including assessing systematic bias, standard error of measurement and coefficient of variation. Judgement of the intraclass correlation coefficient was based on Portney and Watkins (2009) with values > 0.75 indicative of good reliability.

14.1.2 Reliability of posture in healthy participants

14.1.2.1 Participants

Twenty normal healthy participants were recruited from the population of staff and students from the School of Healthcare Sciences, Cardiff University. Ethical approval was provided by School of Healthcare Sciences Research Ethics Committee. Inclusion criterion was ability to follow instructions in English. Exclusion criteria were inability to sit unsupported for 1 minute and known difficulties in swallowing.

14.1.2.2 Protocol

(i) Explanation of study, informed consent attained

(ii) Positioning of surface markers:

L4: The 10th ribs were palpated and the lower edge identified. A perpendicular line was run (imaginary) from the lowest edge of the 10th rib to the spinal column. This was identified as L1. Counting down the spinal processes identified L4. This was confirmed by drawing an imaginary perpendicular line from the iliac crests – Tuffier's line (Jung et al. 2004). A reflective marker was placed on L4.

C7: C7 and C6 were identified by visual inspection. C7 was confirmed by asking the participant to extend the neck, C7 remains palpable, C6 is unpalpable (Field and Hutchinson 2006). A reflective marker was placed on C7.

Tragus: A coloured circle was placed on the tragus, using visual inspection.

(iii) The participant sat in a standard wheelchair, with the back and side removed, in a relaxed comfortable position.

(iv) A video camera was set up in line with the participant in the chair, ensuring that the whole trunk was within view. A video recording was taken for 1 minute. Spirit levels within the tripod were used to ensure the camera was horizontal.

(v) Surface markers were removed.

(vi) The participant moved to a supported chair and rested for five minutes

(vii) Steps (ii) to (vi) were repeated 3 times, thus ensuring a time gap and movement between measurements.

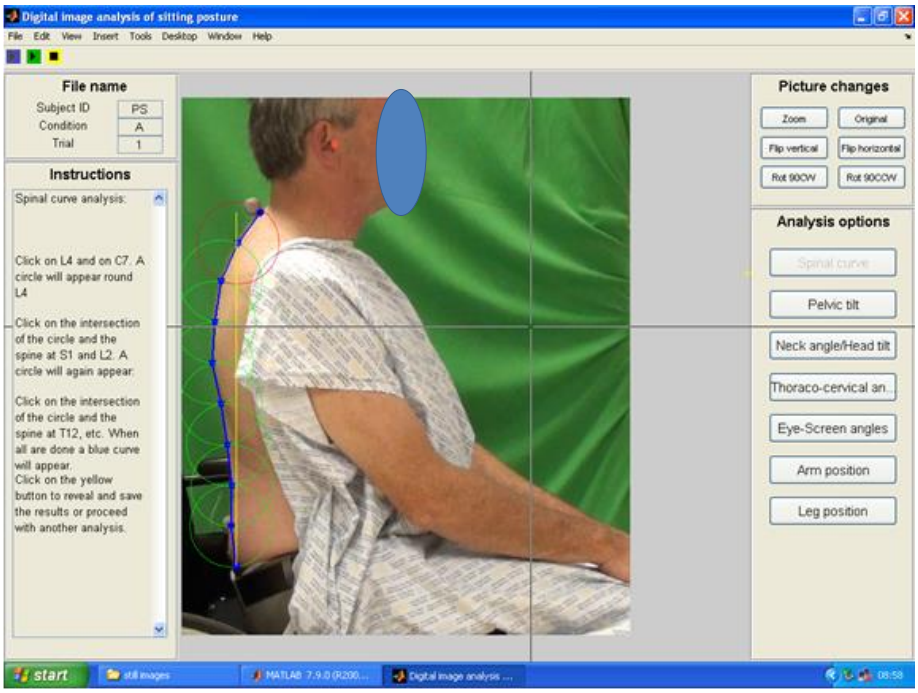
14.1.2.3 Data Processing

Thoracic angle, neck angle and head tilt were processed using a bespoke MATLAB programme (written by Dr Robert van Deursen 2010) and the measures were each a single angle. Still images were taken from the video using Pinnacle Studio software. The still images were then opened within the MATLAB programme and cropped to have a close up view of the relevant area. The appropriate variable was chosen from the MATLAB menu and the instructions followed to measure thoracic angle, neck angle and head tilt. Neck angle was measured using trunk angle as the reference line. Thoracic angle was assessed using the following instructions, see Figure.1.

- Click on L4 and C7. A circle will appear round L4;
- Click on the intersection of the circle and the spine at S1 and L2, a circle will appear again;

- Click on the intersection of the circle and the spine at T12, etc. When all are done, a blue curve will appear;
- Click on the yellow button to reveal and save the results.

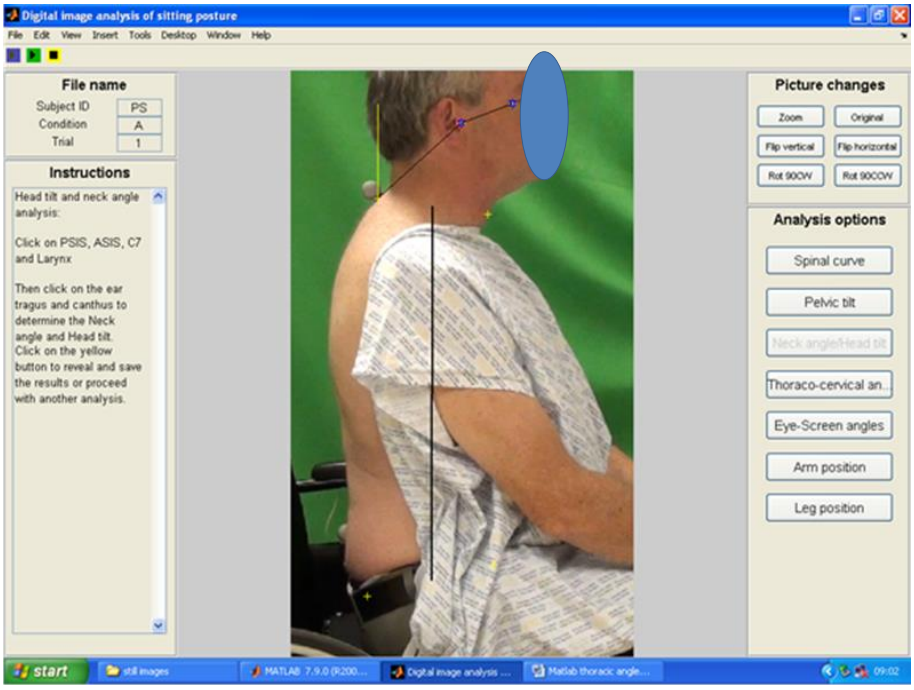
Figure A1.1 Assessing thoracic angle using MATLAB



Head tilt and neck angle were assessed using the following instructions, see FigureA1.2.

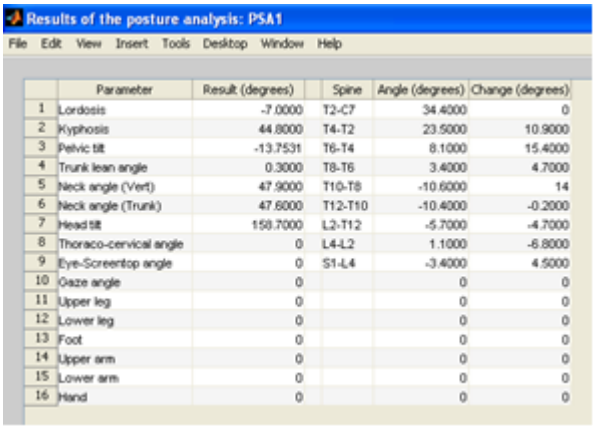
- Click on PSIS, ASIS, C7 and larynx;
- Then click on the ear tragus and eye canthus to determine head tilt and neck angle.

Figure A1.2 Assessing head tilt and neck angle using MATLAB



The output from the MATLAB programme, see FigureA1.3 was recorded.

Figure A1.3 Output from MATLAB posture analysis



Results of the posture analysis: PSA1

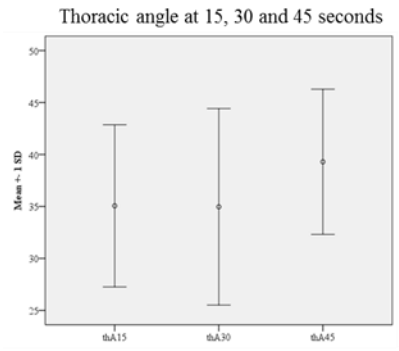
File Edit View Insert Tools Desktop Window Help

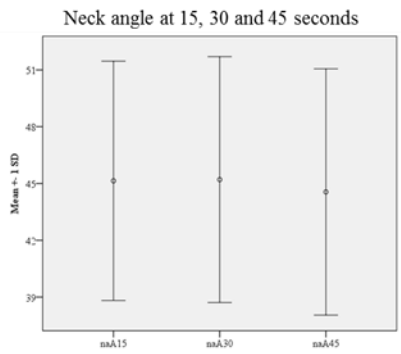
	Parameter	Result (degrees)	Spine	Angle (degrees)	Change (degrees)
1	Lordosis	-7.0000	T2-C7	34.4000	0
2	Kyphosis	44.8000	T4-T2	23.5000	10.9000
3	Pelvic tilt	-13.7531	T6-T4	8.1000	15.4000
4	Trunk lean angle	0.3000	T8-T6	3.4000	4.7000
5	Neck angle (Vert)	47.9000	T10-T8	-10.6000	14
6	Neck angle (Trunk)	47.6000	T12-T10	-10.4000	-0.2000
7	Head tilt	158.7000	L2-T12	-5.7000	-4.7000
8	Thoraco-cervical angle	0	L4-L2	1.1000	-6.8000
9	Eye-Screentop angle	0	S1-L4	-3.4000	4.5000
10	Gaze angle	0		0	0
11	Upper leg	0		0	0
12	Lower leg	0		0	0
13	Foot	0		0	0
14	Upper arm	0		0	0
15	Lower arm	0		0	0
16	Hand	0		0	0

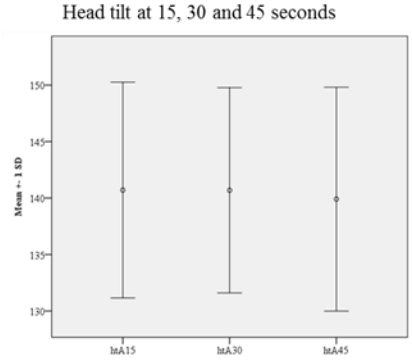
14.1.2.4 Data Analysis

Sitting posture was recorded by video camera for one minute, with a still image to be extracted when posture was stable. In order to determine at which time point during the video recording that the still image could be taken, images were extracted at 15, 30 and 45 seconds from the beginning of the recording. Analysis of mean and standard deviations values at the three time points indicated that the most stable time for the still image to be taken was at 30 seconds, see Figure A1.4

Figure A1.4 Posture at 15, 30 and 45 seconds







Reliability was assessed using repeated measures analysis of variance (ANOVA); standard error of the mean (SEM); coefficient of variation (CV) and intraclass correlation coefficients (ICC) – two way mixed model with measures of consistency (3,1).

14.1.2.5 Results

Twenty healthy participants took part in the reliability study. The demographic details are shown in **Error! Reference source not found.**A1.1. The results of the analyses are shown in **Table** A1.2.

Table A1.1 Demographic data of healthy subjects in posture reliability study

	Mean ±sd	**Minimum**	**Maximum**
Height (cm)	169.28 ±6.72	159.00	188.00
Weight (Kg)	73.72 ±20.30	46.90	138.20
BMI (Kg/m^2)	25.46 ±5.26	17.87	39.10
Age (years)	35.95 ±13.82	19.00	59.00

n=20

BMI Body mass index

Table A1.2 Reliability: digital analysis of posture in healthy control subjects

Variable	**Repeated measures ANOVA**	**SEM (√MSE)**	**CV (SEM/mean)*100**	**ICC**
Thoracic angle (degrees) (single measure)	F=0.463, p=0.633	4.61º	12.9%	0.718
Thoracic angle (degrees) (average measure)	F=144.9, p<0.001	3.61º	8.8%	0.943
Neck angle (degrees)	F=2.144, p=0.144	2.41º	5.43%	0.907
Head til (degrees)t	F=0.514, p=0.602	3.56º	2.54%	0.839

ANOVA Analysis of variance

SEM Standard error of measurement

MSE Mean square error

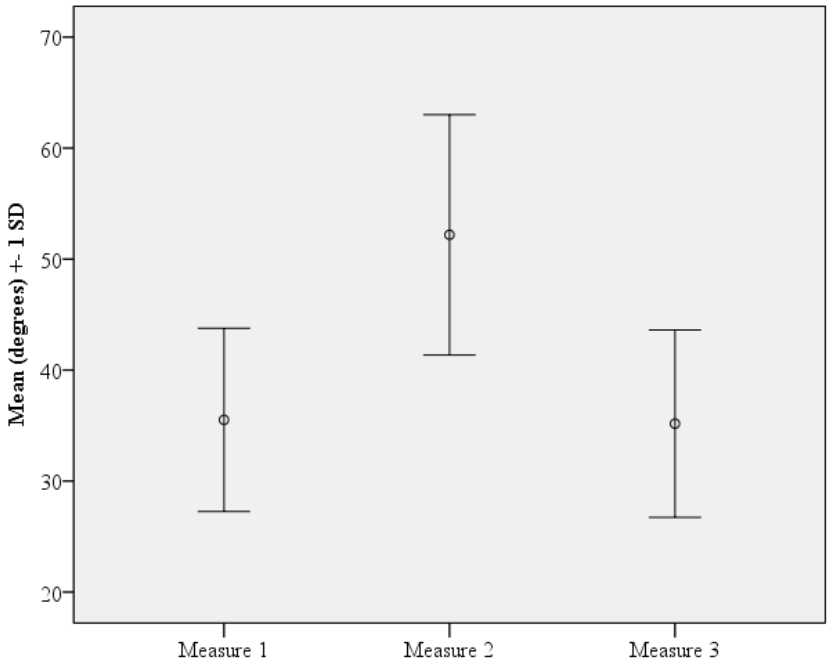
CV Coefficient of variation

ICC Intraclass correlation coefficient

As the CV was high and ICC <0.75 for thoracic angle when measured by a single measure, further analysis was carried out whereby the average of three readings were used for thoracic angle. SEM, CV and ICC all improved by using the average value, but a systematic error was

apparent, with the second occasion reading being significantly higher than both first and third readings, see Figure A1.5.

Figure A1.5 Consistency of averaged thoracic angle readings



On reviewing the raw data, it is not clear why this systematic error occurred. Further exploration of the reliability of this method was then carried out with a sample of people with HD.

14.1.3 Reliability of posture in people with Huntington's disease

14.1.3.1 Participants

Images from 20 participants in the observational study were used to determine reliability of digital analysis for posture in people with HD.

14.1.3.2 Protocol

Data were collected from the participants following the protocol described in section 14.1.2.2. The images were analysed on separate occasions during one day.

14.1.3.3 Data processing and analysis

Data were processed and analysed as described in section 14.1.2.3.

14.1.3.4 Results

Data from 20 participants with HD were used for the reliability study. One assessor measured thoracic angle, neck angle and head tilt from the video recording on three occasions within one day as per protocol for the healthy control reliability study. Based on the high SEM and CV and low ICC using a single measure for thoracic angle, the value for thoracic angle was the average of three readings. The demographic data of the participants are in **Error! Reference source not found.**A1.3.

Table A1.3 Demographic data of subjects with HD in posture reliability study

	Mean ±sd	**Minimum**	**Maximum**
Height (cm)	170.25 ±10.07	147.00	184.00
Weight (Kg)	68.85 ±11.19	48.90	84.50
BMI (Kg/m^2)	23.67 ±2.77	19.94	29.21
Age (years)	49.95 ±11.23	25.00	70.00

n=20

BMI Body mass index

The results of the analyses are shown in Table A1.4. The ICC values indicate excellent reliability and were higher than those from the reliability in healthy subjects. This may be due to the increased range in values of thoracic angle in people with HD compared to healthy subjects, the greater variance between subjects in relation to within subject variance resulting in a higher ICC. This is then reflected in lower SEM and CV. The systematic error seen in the study with healthy subjects was not apparent in the study with people with HD, see Figure A1.6.

Table A1.4 Reliability: digital analysis of posture in people with HD

Angle	**ANOVA**	**SEM √MSE**	**CV (SEM/mean)*100**	**ICC**
Thoracic angle (degrees) (average)	F=2.236 p=0.121	1.55º	2.73%	0.996
Neck angle (degrees)	F=1.214 p=0.308	1.18º	2.12%	0.998
Head tilt (degrees)	F=0.634 p=0.536	2.43º	1.87%	0.997

ANOVA Analysis of variance

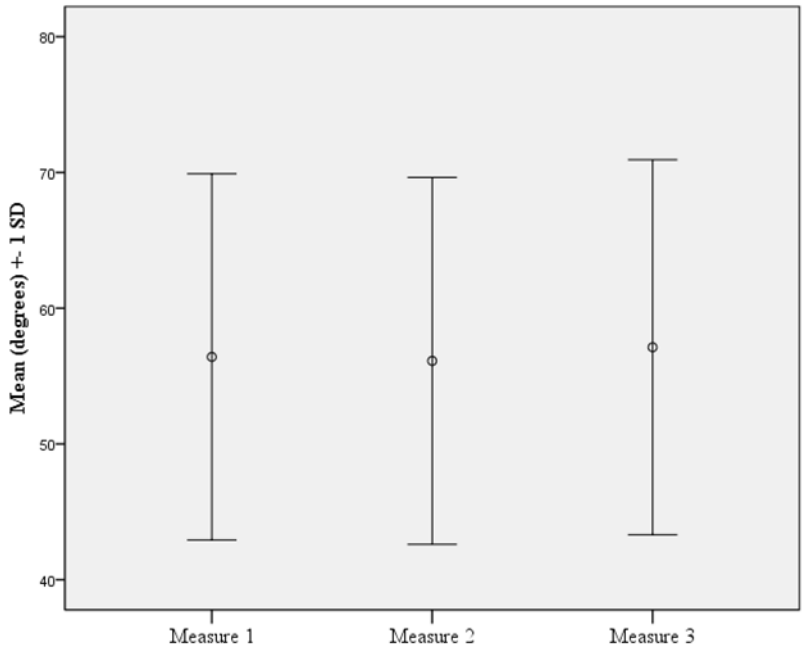
SEM Standard error of measurement

MSE Mean square error

CV Coefficient of variation

ICC Intraclass correlation coefficient

Figure A1.6 Consistency of thoracic angle readings in people with Huntington's disease



14.1.4 Summary of reliability study

The analyses indicated that the method of measuring posture by digital analysis and bespoke MATLAB software used by the researcher was reliable in measuring thoracic posture, neck angle and head tilt in people with HD.

A kyphotic posture reduces lung volumes (Harrison et al. 2007) and in particular FVC (Lin et al. 2006) and minute volumes (Landers et al. 2003) and therefore may be an influencing factor in respiratory function in people with HD. A range of instruments and techniques are available for measuring posture and have been shown to be reliable e.g. magnetic tracking devices (Jordan et al. 2000) spinal wheel (Sheeran et al. 2010) and spinal mouse (Mannion et al. 2004). Digital analysis has been suggested as an alternative gold standard to radiographic imaging (van Niekerk et al. 2008) which obviously reduces the exposure to X-rays and is more convenient for clinical and/or home based studies. The results from this study demonstrated a SEM of 1.55º for thoracic angle which is comparable to 1.12º mean difference noted by Van Niekerk (2008). This protocol for taking still images from a video enables analysis of posture in people with a movement disorder that is reliable, non-invasive and convenient for use within a clinic or home setting and was therefore deemed appropriate for use within the observation study

14.2 Appendix 2 Ethical and Research and Development approval

Research Ethics Committee for Wales

REC for WALES

Churchill House, Fourth Floor, 17 Churchill Way, Cardiff, CF10 2HX
Tŷ Churchill, 17 Heol Churchill, Caerdydd, CF10 2HX

31 October 2008

Mrs Una Jones
Department of Physiotherapy,
SOHCS
Cardiff University
Heath Park
Cardiff CF14 4XN

Dear Mrs Jones

Full title of study: **Respiratory function in people with Huntington's disease: a cross sectional study**
REC reference number: **08/MRE09/65**

Thank you for your letter of 16 October 2008, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chairman.

Confirmation of ethical opinion
On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Mental Capacity Act 2005
I confirm that the committee has approved this research project for the purposes of the Mental Capacity Act 2005. The committee is satisfied that the requirements of section 31 of the Act will be met in relation to research carried out as part of this project on, or in relation to, a person who lacks capacity to consent to taking part in the project.

Ethical review of research sites
The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the research site(s) taking part in this study. The favourable opinion does not therefore apply to any site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at sites requiring SSA.

Conditions of the favourable opinion
The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Approved documents
The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Research team CVs		
~~Participant Consent Form~~ **Superseded**	~~1~~	~~04 June 2008~~
Participant Information Sheet: Healthy subjects	1	09 May 2008
~~Participant Information Sheet: Participants unable to consent~~ **Superseded**	~~1~~	~~09 May 2008~~
~~Participant Information Sheet: HD Group~~ **Superseded**	~~1~~	~~09 May 2008~~
GP/Consultant Information Sheets	1	16 May 2008
Questionnaire: Perceptions questionnaire - nominated consultee	1	23 May 2008
Questionnaire: Perceptions questionnaire	1	23 May 2008
Compensation Arrangements		29 August 2008
Letter from Sponsor	SPON579-08-Busse	05 June 2008
Summary/Synopsis	1	04 June 2008
Covering Letter	signed by Mrs Una Jones	11 September 2008
Protocol	1	23 May 2008
Investigator CV		11 September 2008
Application	1.0	10 September 2008
Response to Request for Further Information	letter signed Dr Jones	16 October 2008
Participant Consent Form	2	10 October 2008
Participant Information Sheet: Participants with Huntington's Disease who are unable to give consent	2	10 October 2008
Participant Information Sheet: Participants with Huntington's Disease	2	10 October 2008

Statement of compliance
The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review
Now that you have completed the application process please visit the National Research Ethics Website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

08/MRE09/65	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Dr Gordon Taylor
Chairman

Email: corinne.scott@bsc.wales.nhs.uk

Enclosures: "After ethical review – guidance for researchers"
Site approval form

Copy to: Mr Chris Shaw

NISCHR

Uned Cydlynu Caniatâd | PCU | Permissions Co-ordinating Unit

Research Ethics Committee (REC) for Wales
Sixth Floor, Churchill House
17 Churchill Way
Cardiff CF10 2TW
Telephone : 029 2037 6529
Fax : 029 2037 6524

E-mail : corinne.scott@wales.nhs.uk

Website : www.nres.nhs.uk

21 July 2011

Mrs Una Jones
School of Healthcare Studies
Cardiff University
Heath Park
Cardiff CF14 4XN

Dear Mrs Jones

Study title:	**Feasibility and benefit of inspiratory muscle training in people with Huntington's disease.**
REC reference:	**11/WA/0183**
Protocol number:	**SPON975-11**

Thank you for your letter of 14 July 2011, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chairman, Dr. Gordon Taylor.

Confirmation of ethical opinion
On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites
The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites
The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion
The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents
The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Covering Letter	signed Mrs Jones	08 June 2011
Evidence of insurance or indemnity	Zurich Municipal certificate of Insurance - Cardiff University - expires 31 July 2011	27 July 2010
GP/Consultant Information Sheets	1	16 May 2011
Interview Schedules/Topic Guides	1	26 May 2011
Investigator CV	Mrs Jones	08 June 2011
Investigator CV	Dr Monika Busse	20 May 2011
Investigator CV	Dr Stephanie Enright	18 May 2011
Letter from Sponsor	signed Dr KJ Pittard-Davies, Cardiff University	03 June 2011
Letter from Statistician	Email from Robert Newcombe, Cardiff University	18 May 2011
Letter of invitation to participant	1	16 May 2011
Participant Consent Form	1	26 May 2011
Participant Information Sheet	2	11 July 2011
Protocol	2	11 July 2011
REC application	signed in ink by Mrs Jones; electronically by Matthew Harris, sponsor's representative; in ink by Stephanie Enright and Monica Busse, academic supervisors	06 June 2011
Response to Request for Further Information	Email from Mrs. Jones	14 July 2011
Summary/Synopsis	1	26 May 2011

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements
The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback
You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

11/WA/0183	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Dr Gordon Taylor
Chairman

Email: corinne.scott@wales.nhs.uk

Enclosures: "After ethical review – guidance for researchers"
Copy to: Mr Chris Shaw
Prof Jonathan Bisson, Cardiff And Vale University Health Board

NHS WALES GIG CYMRU

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Ein cyf/Our ref
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Fax: 029 20745311
Research.Development@cardiffandvale.wales.nhs.uk

From: Professor MF Scanlon
Trust R&D Director
Radnor House
University Hospital of Wales
Cardiff
CF14 4XW

25 July 2008
Mrs Una Jones
Department Of Physiotherapy, SOHCS
Cardiff University, Heath Park
CF14 4XN

Dear Mrs Jones

Project ID : 08/IBD/4316 : Respiratory function in people with Huntington's disease: a cross sectional study

Thank you for your recent communication regarding the above project, which was reviewed on 25 July 2008 by the Joint Trust/University Peer & Risk Review Committee.

I am pleased to inform you that the project has been approved and that Cardiff University will act as research Sponsor under the Research Governance Framework for Health and Social Care. Cardiff & Vale NHS Trust is therefore happy for the project to begin, subject to:

1) Approval from the appropriate NHS Research Ethics Committee
2) Honorary Contracts, where required, being in place before the research begins.

Please ensure that the appropriate Research Ethics Committee have a copy of this letter. Once you have gained ethical approval, please forward a copy of the approval letter to the Research and Development Office at the above address.

The committee felt that this project has been well thought through and written up. In addition the particular issues around informed consent in this vulnerable group have been recognised and dealt with appropriately.

However, the committee also requested that you take the following comments into consideration:

1. As Huntington's disease progresses, dystonic movements and generalised change in muscle tone may make the assessment of lung function tests difficult to interpret.

2. Smoking history is recorded, but there is no information on how the investigators propose to use this. In all comparisons of respiratory parameters between patients and controls or between stages of the disease, these parameters should be expressed relative to normative values for gender, age and body size, of course. But also, analyses should be developed that take into account any differences in smoking status as a confounder.

May I take this opportunity to wish you success with the project and remind you that as Principal Investigator you are required to:

- Inform the Trust R&D Office if any external or additional funding is awarded for this project in the future.
- Inform the Trust R&D Office of any amendments relating to the protocol, including personnel changes and amendments to the actual or anticipated start / end dates.
- Complete any documentation sent to you by the Trust R & D Office or University Research & Commercial Division regarding this project.
- Ensure that adverse event reporting is in accordance with Cardiff and Vale NHS Trust Policy and Procedure for Reporting Research-Related Adverse Events (Refs 164 & 174) and the Trust Incident Reporting and Investigation Procedure (Ref 108).
- Undertake the project in accordance with ICH-GCP.
- Adhere to the protocol as approved by the Research Ethics Committee.
- Ensure the research complies with the Data Protection Act 1998.

Yours sincerely,

Professor MF Scanlon
Chair of the Joint Trust/University Peer & Risk Review Committee

CC Chris Shaw, Research and Commercial Division, Cardiff University
CC R&D Lead Dr I M Frayling

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GIG CYMRU NHS WALES
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Ein cyf/Our ref
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Fax: 029 20745311
CAV_research.development@wales.nhs.uk

From: Professor Jonathan I Bisson
R&D Director
Research & Development Office
2TB2 Room 1
University Hospital of Wales
Cardiff
CF14 4XW

24 August 2011

Mrs Una Jones
School of Healthcare Studies
TY Dewi Sant
Heath Park
Cardiff
CF14 4XN

Dear Mrs Jones

Project ID: 11-IBD-5200: Feasibility And Benefit Of Inspiratory Muscle In People With Huntington's Disease

Thank you for your recent communication informing us about the above research project, and for supplying the following documentation:

Document	Version	Date
NHS RD Form	3.1	Received 08/08/11
SSI		
Protocol	2.0	11/07/11
Letter to GP	1.0	16/05/11
Interview Schedule	1.1	26/05/11
Information Sheet	2.0	11/07/11
Consent Form	1.0	26/05/11

Prepared by Emma Lewis, R&D Coordinator *Version 2.0, 26-04-10*

Where the only involvement of an NHS organisation in a project is as a Participant Identification Centre, NHS R&D approval is not required. We will however retain a copy of your project documentation on file. I am pleased to therefore confirm that Cardiff & Vale University Local Health Board has no objections to acting as a Participant Identification Centre for this project.

Before beginning your study, please ensure that you have approval from the appropriate NHS Research Ethics Committee.

Please ensure that you supply the appropriate research site/s with a copy of this letter.

May I take this opportunity to wish you success with the project and remind you that this letter relates only to Cardiff & Vale UHB undertaking the role of Participant Identification Centre for this study. You must inform the R&D Office if:

- You wish to seek approval for Cardiff & Vale UHB to undertake any participant-related research procedures specified in the study protocol (including taking informed consent for participation) and therefore become a research site for this study
- You make any amendments relating to the protocol, including personnel changes and amendments to the actual or anticipated start / end dates
- You would like Cardiff & Vale UHB to refer potential participants to any research sites in this study other than those listed above.
- You would like Cardiff & Vale UHB to act as a Participant Identification Centre for any research other than the above-named project.

Procedures for participant identification must comply with the Data Protection Act 1998. For further advice and information please contact Mr Nic Drew, Data Protection Officer on 029 20746677 or email Nic.Drew@wales.nhs.uk.

Yours sincerely,

Professor Jonathan I Bisson
R&D Director

CC Local collaborator, Prof Anne Rosser

14.3 Appendix 3 Standard operating procedures

14.3.1 Unified Huntington's Disease Rating Scale: Total Motor Score (UHDRS:TMS)

REGISTRY V3
UNIFIED HUNTINGTON'S DISEASE RATING SCALE '99 - MOTOR ASSESSMENT

Study Site: ☐☐☐ Subject: ☐☐☐ ☐☐☐ ☐☐☐☐

Examiner: ☐☐☐☐ Date info obtained: ☐☐ - ☐☐ - ☐☐☐☐ (D D - M M - Y Y Y Y)

All items must be completed. Use U if information is unavailable. Use N if information is not applicable.

General

Motor score: ☐☐☐

Motor Assessment

Ocular pursuit:

0 = complete (normal)
1 = jerky movement
2 = interrupted pursuits/full range
3 = incomplete range
4 = cannot pursue

Horizontal ☐ Vertical ☐

Saccade initiation:

0 = normal
1 = increased latency only
2 = suppressible blinks or head movements to initiate
3 = unsupressable head movements
4 = cannot initiate saccades

Horizontal ☐ Vertical ☐

Saccade velocity:

0 = normal
1 = mild slowing
2 = moderate slowing
3 = severely slow, full range
4 = incomplete range

Horizontal ☐ Vertical ☐

Dysarthria: ☐

0 = normal
1 = unclear, no need to repeat
2 = must repeat to be understood
3 = mostly incomprehensible
4 = anarthria

Tongue protrusion: ☐

0 = can hold tongue fully protruded for 10 sec
1 = cannot keep fully protruded for 10 sec
2 = cannot keep fully protruded for 5 sec
3 = cannot fully protrude tongue
4 = cannot protrude tongue beyond lips

Finger taps:

0 = normal (≥15/5 sec.)
1 = mild slowing, reduction in amplitude (11-14/5 sec.)
2 = moderately impaired (7-10/5 sec.)
3 = severely impaired (3-6/5 sec.)
4 = can barely perform task (0-2/5 sec.)

Right ☐ Left ☐

Pronate/supinate-hands:

0 = normal
1 = mild slowing and/or irregular
2 = moderate slowing and irregular
3 = severe slowing and irregular
4 = cannot perform

Right ☐ Left ☐

1 / 3

REGISTRY V3
UNIFIED HUNTINGTON'S DISEASE RATING SCALE '99 - MOTOR ASSESSMENT

Study Site: ☐☐☐ Subject: ☐☐☐ ☐☐☐ ☐☐☐☐

Examiner: ☐☐☐☐ Date info obtained: ☐☐.☐☐.☐☐☐☐ (D D . M M . Y Y Y Y)

All items must be completed. Use U if information is unavailable. Use N if information is not applicable.

Luria: ☐

0 = ≥4 in 10 sec, no cue
1 = <4 in 10 sec, no cue
2 = ≥4 in 10 sec with cues
3 = <4 in 10 sec with cues
4 = cannot perform

Rigidity-arms:

0 = absent
1 = slight or present only with activation
2 = mild to moderate
3 = severe, full range of motion
4 = severe with limited range

Right ☐ Left ☐

Bradykinesia-body: ☐

0 = normal
1 = minimally slow (?normal)
2 = mildly but clearly slow
3 = moderately slow, some hesitation
4 = markedly slow, long delays in initiation

Maximal dystonia:

0 = absent
1 = slight/intermittent
2 = mild/common or moderate/intermittent
3 = moderate/common
4 = marked/prolonged

Trunk ☐
RUE ☐
LUE ☐
RLE ☐
LLE ☐

Maximal chorea:

0 = absent
1 = slight/intermittent
2 = mild/common or moderate/intermittent
3 = moderate/common
4 = marked/prolonged

Face ☐
BOL ☐
Trunk ☐
RUE ☐
LUE ☐
RLE ☐
LLE ☐

Gait: ☐

0 = normal gait, narrow base
1 = wide base and/or slow
2 = wide base and walks with difficulty
3 = walks only with assistance
4 = cannot attempt

Study Site: | | | |

Examiner: | | | | |

Subject: | | | | | | | | | | |

Date info obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if information is unavailable. Use N if information is not applicable.

Tandem walking: | |

0 = normal for 10 steps
1 = 1 to 3 deviations from straight line
2 = >3 deviations
3 = cannot complete
4 = cannot attempt

Retropulsion pull test: | |

0 = normal
1 = recovers spontaneously
2 = would fall if not caught
3 = tends to fall spontaneously
4 = cannot stand

Diagnostic Confidence

Diagnostic confidence level: | |

0 = Normal (no abnormalities)
1 = non-specific motor abnormalities (less than 50 % confidence)
2 = motor abnormalities that may be signs of HD (50 - 89 % confidence)
3 = motor abnormalities that are likely signs of HD (90 - 98 % confidence)
4 = motor abnormalities that are unequivocal signs of HD ≥ 99 % confidence)

14.3.3 Unified Huntington's Disease Rating Scale:Total Functional Capacity (UHDRS:TFC)

REGISTRY V3
UNIFIED HUNTINGTON'S DISEASE RATING SCALE '99 - TOTAL FUNCTIONAL CAPAC

Study Site: ☐☐☐ Subject: ☐☐☐ ☐☐☐ ☐☐☐

Examiner: ☐☐☐☐ Date info obtained: ☐☐ - ☐☐ - ☐☐☐☐ (D D - M M - Y Y Y Y)

All items must be completed. Use U if information is unavailable. Use N if information is not applicable.

General

Functional score: ☐☐☐

Functional Capacity

Occupation: ☐

0 = unable
1 = marginal work only
2 = reduced capacity for usual job
3 = normal

Finances: ☐

0 = unable
1 = major assistance
2 = slight assistance
3 = normal

Domestic chores: ☐

0 = unable
1 = impaired
2 = normal

ADL: ☐

0 = total care
1 = gross tasks only
2 = minimal impairment
3 = normal

Care level: ☐

0 = full time skilled nursing
1 = home or chronic care
2 = home

Information Sources:

Was the information obtained from: ☐

1 = participant only
2 = participant and family/companion

Adopted from 1999 Huntington Study Group. 1 / 1

14.3.4 Unified Huntington's Disease Rating Scale Functional Assessment

REGISTRY V3
HUNTINGTON'S DISEASE RATING SCALE '99 - FUNCTIONAL ASSESSMENT

Study Site: ☐☐☐
Examiner: ☐☐☐☐
Subject: ☐☐☐ ☐☐☐ ☐☐☐☐
Date info obtained: ☐☐ D D . ☐☐ M M . ☐☐☐☐ Y Y Y Y

All items must be completed. Use U if information is unavailable. Use N if information is not applicable.

General

Functional Assessment Score: ☐☐

Functional Assessment

For the next 25 questions, please use:
1 = yes
0 = no

Could subject engage in gainful employment in his/her accustomed work: ☐
Could subject engage in any kind of gainful employment? ☐
Could subject engage in any kind of volunteer or non-gainful work? ☐
Could subject manage his/her finances (monthly) without any help? ☐
Could subject shop for groceries without help? ☐
Could subject handle money as a purchaser in a simple cash (shop) transaction? ☐
Could subject supervise children without help? ☐
Could subject operate an automobile safely and independently? ☐
Could subject do his/her own housework without help? ☐
Could subject do his/her own laundry (wash/dry) without help? ☐
Could participant prepare his/her own meals without help? ☐
Could subject use the telephone without help? ☐
Could subject take his/her own medications without help? ☐
Could subject feed himself/herself without help? ☐
Could subject dress himself/herself without help? ☐
Could subject bathe himself/herself without help? ☐
Could subject use public transportation to get places without help? ☐
Could subject walk to places in his/her neighbourhood without help? ☐
Could subject walk without falling? ☐
Could subject walk without help? ☐
Could subject comb hair without help? ☐
Could subject transfer between chairs without help? ☐
Could subject get in and out of bed without help? ☐
Could subject use toilet/commode without help? ☐

Adopted from 1999 Huntington Study Group. 1 / 2

14.3.5 Barthel Index

Instructions to subject/carer

This questionnaire will ask some questions about whether you can do everyday activities on your own or whether you need help with them. I would like you to answer the questions on how you have carried out the following activities over the last few days.

Activity Score

FEEDING

0 = unable

5 = needs help cutting, spreading butter, etc., or requires modified diet

10 = independent _____

BATHING

0 = dependent

5 = independent (or in shower) _____

GROOMING

0 = needs to help with personal care

5 = independent face/hair/teeth/shaving (implements provided) _____

DRESSING

0 = dependent

5 = needs help but can do about half unaided

10 = independent (including buttons, zips, laces, etc.) _____

BOWELS

0 = incontinent (or needs to be given enemas)

5 = occasional accident _____

BLADDER

0 = incontinent, or catheterized and unable to manage alone

5 = occasional accident

10 = continent _____

TOILET USE

0 = dependent

5 = needs some help, but can do something alone

10 = independent (on and off, dressing, wiping) _____

TRANSFERS (BED TO CHAIR AND BACK)

0 = unable, no sitting balance

5 = major help (one or two people, physical), can sit

10 = minor help (verbal or physical)

15 = independent _____

MOBILITY (ON LEVEL SURFACES)

0 = immobile or < 50 yards

5 = wheelchair independent, including corners, > 50 yards

10 = walks with help of one person (verbal or physical) > 50 yards

15 = independent (but may use any aid; for example, stick) > 50 yards _____

STAIRS

0 = unable

5 = needs help (verbal, physical, carrying aid)

10 = independent _____

TOTAL (0–100): _____

Provided by the Internet Stroke Center — www.strokecenter.org

The Barthel ADL Index: Guidelines

1. The index should be used as a record of what a patient does, not as a record of what a patient could do.

2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.

3. The need for supervision renders the patient not independent.

4. A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives and nurses are the usual sources, but direct observation and common sense are also important. However direct testing is not needed.
5. Usually the patient's performance over the preceding 24-48 hours is important, but occasionally longer periods will be relevant.
6. Middle categories imply that the patient supplies over 50 per cent of the effort.
7. Use of aids to be independent is allowed.

References

Mahoney FI, Barthel D. “Functional evaluation: the Barthel Index.”
Maryland State Medical Journal 1965;14:56-61. Used with permission.
Loewen SC, Anderson BA. “Predictors of stroke outcome using objective measurement scales.” Stroke. 1990;21:78-81.
Gresham GE, Phillips TF, Labi ML. “ADL status in stroke: relative merits of three standard indexes.”Arch Phys Med Rehabil. 1980;61:355-358.
Collin C, Wade DT, Davies S, Horne V. “The Barthel ADL Index: a reliability study.”
Int Disability Study.1988;10:61-63.

Copyright Information

14.3.6 Respiratory History and Swallow questionnaire

Based on Hart and Polkey 2001 and Wiles and Hughes 1996

1. Have you visited the GP in the last year in relation to breathing problems?

If yes, how many times, what was the main problem and how was this managed?

2. Have you had any breathing problems that you did not go to the GP about?

If yes, how many times, what was the main problem and how was this managed?

3. Do you smoke? If yes, how many cigarettes do you smoke in a day?
4. Have you had a flu vaccination in the last year?
5. Do you ever get breathless? If yes, when do you get breathless e.g. on walking/ walking uphill/ lying flat/sitting?
6. Do you have any problems sleeping? Do you feel sleepy during the day or have morning headaches?
7. Do you have any problems swallowing?
8. Has your voice changed over the last year?
9. Do you need to be careful when eating?
10. Do you avoid certain foods?
11. Do you have difficulty keeping food or drink in your mouth?
12. Does your food need special preparation?
13. Do you need a glass of water when you are eating?
14. Do you cough when you are eating?
15. Does food or drink go down the wrong way?
16. Do you get short of breath when you are eating?

14.3.7 Lung function tests

From Miller et al (2005)

Instructions FVC, FEV_1:

The following tests will assess how much you can breathe in and out of your lungs. You will need to take as big a breath in as you can and then blow into the machine as hard and as long as you can. You will do this about 3-5 times to ensure we get the best result for you.
Demonstrate and practice with viral mouthpiece.

Perform manoeuvre:
Have subject assume the correct position – sitting upright, head slightly elevated;
Attach nose clip;
Inhale completely and rapidly with a pause of <1 second at TLC;
Place mouthpiece in mouth and close lips around the mouthpiece;
Exhale maximally until no more air can be expelled while maintaining an upright posture;
Repeat instructions as necessary, coaching vigorously;
Repeat for a minimum of three manoeuvres – no more than eight are usually required.

A manoeuvre is acceptable if:
It is free from artefacts – cough, early termination of test, effort not maximal, leak in equipment.
Satisfactory exhalation – duration of >6sec (3 sec for children), if the subject cannot or should not continue to exhale.

After 3 acceptable manoeuvres resulting in 3 spirograms have been obtained the following criteria must apply:
The 2 largest FVC must be within 0.150 L of each other.
The 2 largest FEV_1 must be within 0.150 L of each other.
If both these criteria are met, the test session may be concluded.
If both these criteria are not met, continue testing until
both criteria are met or;
a total of 8 tests have been performed (optional) or;
the subject cannot or should not continue.

Instructions PEF

Perform manoeuvre:

Ask subject to assume correct position – neck must be in neutral;

Inspire maximally and deliver the blow without hesitation.

The use of a nose clip is not necessary. For safety reasons, testing should be preferably done in the sitting position, using a chair without arms and without wheels. If testing is undertaken in a different position, this must be documented.

A manoeuvre is acceptable if:

A good seal has been achieved;

No hesitation has occurred;

No abnormal start to the manoeuvre.

After 3 acceptable manoeuvres have been performed the following criterion must apply:

- The 2 largest PEF must be within 0.67 l/sec of each other.

If this does not apply up to 2 additional blows van be performed.

Instructions PEF Cough

The subject will be seated comfortably and the test explained to them. They will complete the following manoeuvre with a peak flow meter:

Take a maximal breath in;

Seal lips around mouthpiece or apply mask firmly to the face;

Cough as hard as possible into the peak flow mouthpiece or mask.

This will be repeated three times and the maximum value recorded.

Instructions Flow Volume loops:

An expiratory flow volume loop is obtained during the FVC/FEV_1 manoeuvre.

Inspiratory flow volume loops are more difficult for the subject and will not be used in the study.

14.3.8 Respiratory muscle testing

From ATS/ERS (2002)

Instructions MIP, MEP

The following tests will measure how strong your respiratory muscles are. You will need to breathe out as much as possible, then place the mouthpiece in your mouth, breath in as much as possible and breathe out as much as possible. You will do this 3-5 times. Demonstrate and practice.

Manoeuvre:

Subject sitting, nose clip not required,

Breathe out as much as possible.

Place flanged mouthpiece in mouth.

Breathe in as much as possible, with encouragement.

Breathe out as much as possible with encouragement.

Repeat 3 times.

Ensure maximum values vary less than 20%.

Record the largest measure.

Instructions SNIP

This test will measure how strong your respiratory muscles are by taking a sniff. This catheter will be placed in one nostril and you will sniff through the other nostril. Demonstrate and practice. You will need to take 15 sniffs, with at least 30 sec rest between each sniff.

Manoeuvre:

Subject sitting.

Test which size nose piece fits by placing a catheter in the nostril and asking the subject to sniff. Choose the size with no leak.

Allow 1 minutes rest.

Ask the subject to take as big a sniff as possible.

Repeat 15 times, with at least 30 secs rest between each sniff.

Record the largest pressure.

Single breath work capacity

From Chatham et al (1999)

Instructions to subject:

This test will measure how strong your respiratory muscles are over a long breath in. You will breathe out as much as possible, then breathe in as much as possible for as long as possible. You will repeat this 3 – 5 times. Demonstrate and practice.

Manoeuvre:

Subject sitting, with nose clip in place;

Breathe out as much as possible;

Place flanged mouthpiece in mouth;

Breathe in as much as possible and for as long as possible with encouragement;

Repeat 3 times;

Record highest value.

14.3.9 International Physical Activity Questionnaire – short form.

From IPAQ Research Committee (2005)

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions are about the time you spent being physically active in the last 7 days. They include questions about activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Your answers are important.

Please answer each question even if you do not consider yourself to be an active person.

THANK YOU FOR PARTICIPATING.

In answering the following questions,

"Vigorous" physical activities refer to activities that take hard physical effort and make you breathe much harder than normal.

"Moderate" activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

1a. During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, aerobics, or fast bicycling,?

Think about only those physical activities that you did for at least 10 minutes at a time.

_____ days per week

1b. How much time in total did you usually spend on one of those days doing vigorous physical activities?

_____ hours _____ minutes

or

☐ none

2a. Again, think only about those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do moderate physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

_____ days per week

2b. How much time in total did you usually spend on one of those days doing moderate physical activities?

_____ hours _____ minutes

or

☐ none

3a. During the last 7 days, on how many days did you walk for at least 10 minutes at a time? This includes walking at work and at home, walking to travel from place to place, and any other walking that you did solely for recreation, sport, exercise or leisure.

_____ days per week

3b. How much time in total did you usually spend walking on one of those days?

_____ hours _____ minutes

or

☐ none

The last question is about the time you spent sitting on weekdays while at work, at home, while doing course work and during leisure time. This includes time spent sitting at a desk, visiting friends, reading travelling on a bus or sitting or lying down to watch television.

4. During the last 7 days, how much time in total did you usually spend sitting on a week day?

____ hours _____ minutes

This is the end of questionnaire, thank you for participating.

14.3.10 Borg perceived exertion scale

Borg (1982)

6	No exertion at all
7	Extremely light
8	
9	Very light - (easy walking slowly at a comfortable pace)
10	
11	Light
12	
13	Somewhat hard (It is quite an effort; but can continue)
14	
15	Hard (heavy)
16	
17	Very hard (very strenuous, and you are very fatigued)
18	
19	Extremely hard (You can not continue for long at this pace)
20	Maximal exertion

Patient Instructions for Borg Dyspnoea Scale

Look at the rating scale below while you are engaging in an activity; it ranges from 6 to 20, where 6 means "no exertion at all" and 20 means "maximal exertion." Choose the number from below that best describes your level of exertion. This feeling should reflect how heavy and strenuous the exercise feels to you, combining all sensations and feelings of physical stress, effort, and fatigue.

14.3.11 Modified Borg Dyspnoea Scale

Borg (1970)

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Patient Instructions for Borg Dyspnoea Scale

“This is a scale that asks you to rate the difficulty of your breathing. It starts at number 0 where your breathing is causing you no difficulty at all and progresses through to number 10 where your breathing difficulty is maximal. How much difficulty is your breathing causing you right now?”

14.3.12 30 second sit to stand

Macfarlane et al (2006)

1 The chair-stand test will be administered using a chair without arms, with a seat height of 43cm.
2 The chair will be placed against a wall to prevent it from moving during the test.
3 The test begins with the participant seated in the middle of the chair, back straight, feet approximately shoulder-width apart and placed on the floor slightly posterior to the knees, with one foot slightly in front of the other to help maintain balance when standing.
4 Arms will be crossed at the wrists and held against the chest.
5 At the signal "go" the participant rise to a full stand (body erect and straight) and then returns back to the initial seated position.
6 The participants will be encouraged to complete as many full stands as possible within a 30 second time limit.
7 The participant will be instructed to be fully seated between each stand.
8 While monitoring the participant's performance to assure proper form, the tester will silently count the completion of each full stand.
9 Following a demonstration by the tester, a practice trial of one repetition will be given to check proper form, followed by the 30 second test trial.
10 The score will be the total number of stands executed correctly within 30 second (more than halfway up at the end of 30 second counted as a full stand).
11 Incorrectly executed stands will not be counted.

If subjects are unable to stand up one time without assistance than they can use their hands to assist them in rising and returning to the seated position while following all other procedures as described above. It will be noted that hands were used when recording the assessment data.

(Macfarlane et al. 2006)

14.4 Appendix 4 Instrumentation

14.4.1 Maltron Body Composition Analyser

Frequency	50KHz
Resolution	Measures body fat in increments of 0.1%
Impedance Range	200-1000 Ω
Accuracy	Resistance to within 1.00% +/- 4% across 350-1000%
Ambient Temperature Environment	+10°C to 40°C
Relative Humidity	30% to 75% non-condensing
Atmospheric Pressure	700hPa to 1060hPa
Test Current	0.7mA
Power	1-9V PP3 Battery IEC No. 6LR6L
Battery Current	20mA (approx)
Weight	.230 Kgs (0.51 Lbs) with battery or .180 Kgs (0.397 Lbs) with out battery
Dimensions	145 x 80 x 34mm

Maltron International Ltd
PO Box 15
Rayleigh
Essex SS6 9SN
UK
012668778251

14.4.2 Micromedical Microloop Spirometer

Measurements (forced):

VC, FEV.75, FEV1, FEV3, FEV6, FVC, PEF, FEV.75/VC, FEV.75/FVC,FEV1/VC, FEV1/FVC (FER), FEV3/VC, FEV3/FVC, FEV.75/FEV6, FEV1/FEV6, FEF25 (MEF75), FEF50 (MEF50), FEF75 (MEF25), FEF25-75 (MMEF), FEF50/VC, FEF50/FVC, MMEF/FVC (FEF25-75/FVC), FIV1, FIVC, PIF, FIV1/FIVC (FIR), FIF25 (MIF75), FIF50 (MIF50), FIF75 (MIF25), R50 (FEF50/FIF50), MET25-75, FET, MVV (ind.)

Measurements (relaxed):

EVC, IVC, IC,VT (TV),Ti,Te,Ti/Ttot.,VT/Ti (TV/Ti), IRV, ERV, FR

Predicted Values: Various - depends upon national preference (including NHANESIII)

Transducer: Micro Medical Gold Standard Bi-Directional Digital Volume

Resolution: 10ml volume 0.025L/s flow

Accuracy: +/- 3% to ATS recommendations

Standardisation of Spirometry ATS/ERS 2005

Power Supply: Input: 100-240V AC 50-60Hz Output: 5V 2.0A

Battery Pack: Rechargeable Lithium Polymer 3.7V 1600mAH

Dimensions: 123mm x 81mm x 23mm Transducer 50 x 60 x 90mm

Weight: Excluding transducer : Micro Loop unit 191g, Docking Station 124g

Temperature: The instrument will operate in a uniform environment of 0°C-40°C, out of direct sunlight

Operating Humidity: 30-90% non-condensing

Storage Temperature: -20°C to +70°C

Storage Humidity: 10% to 90% RH

Connectivity: USB 1.1

Micro Medical Ltd

Address: Quayside, Chatham Maritime, Chatham, Kent, ME4 4QY, United Kingdom

Phone: +44 (0)1634 893500

Fax: +44 (0)1634 893600

Email: uksales@micromedical.co.uk

Website: www.micromedical.co.uk

14.4.3 Micromedical RPM

Measurements:

PImax/MIP (Maximal Inspiratory Pressure at the Mouth)

PEmax/MEP (Maximal Expiratory Pressure at the Mouth)

SNIP (Sniff Nasal Inspiratory Pressure)

With Puma:

MRPD (Maximum Rate of Pressure Development)

MRR (Maximum Rate of Relaxation)

Tau

Operating pressure: ±300 cmH_2O (±5PSID)

Burst Pressure: ±700 cmH_2O (±20PSID)

Resolution: 1 cmH_2O

Accuracy: ±3%

Power Supply: Single 9V PP3

Dimensions: 170x60x26mm

Weight:175g (unit); 750g (complete)

Operating temperature: 0°C - 40°C

Operating humidity: 30% - 90% RH

Storage temperature: -20°C - +70°C

Storage humidity: 10% - 90% RH

Micro Medical Ltd

Address: Quayside, Chatham Maritime, Chatham, Kent, ME4 4QY, United Kingdom

Phone: +44 (0)1634 893500

Fax: +44 (0)1634 893600

Email: uksales@micromedical.co.uk

Website: www.micromedical.co.uk

14.4.4 DeVilbiss Respiratory Trainer/RT sport

Measurements

Maximal inspiratory pressure (MIP) cmH_2O

Accumulated area under curve of sustained maximal inspiratory pressure:pressure/time units

Specifications

Handset size: 86x585x267mm

Base station size: 222x222x216mm

Combined weight: approximately 2Kg

Maximum pressure range: -350 cm H_2O

Accuracy: 3% or ±3cmH_2O (whichever is higher)

Infra-red distance: 2m

Reception width: 34º height 1.8m

Internal power source: 9V high capacity rechargeable Nickel Cadmium battery

Electrical requirements: 230V, 50Hz, 25VA

Power consumption: 1.2 Watts

Storage conditions ambient temperature: -20ºC to + 35ºC

Storage conditions relative humidity: 10%-100%

Storage condition atmosphere pressure: 500hPaA to 1060hPaA

DeVilbiss- SUNRISE MEDICAL LTD

High Street

Wollaston

West Midlands

DY8 4PS

14.4.5 The POWERbreathe device

Instructions for use:

The device is made ready for use by turning on and selecting ***start*** from the screen menu.

Inhale as deeply as possible through the mouthpiece and then breathe out until the lungs feel completely empty.

Repeat 30 times.

Once 30 breaths have been taken the ***results*** menu will automatically be displayed. You may view the results and/or turn the machine off.

Cleaning the device

After each training session remove the valve head and soak in warm water for 10 minutes. Then hold the valve head under running water whilst opening and closing the valve to aid cleaning of the valve surfaces.

Once a week soak the valve head in a mild sterilising fluid e.g. Milton for 10 minutes. Then hold the valve head under running water whilst opening and closing the valve to aid cleaning of the valve surfaces.

If you are suffering from a cold or respiratory infection, soak the valve head in mild sterilising fluid for 10 minutes after each session. Then hold the valve head under running water whilst opening and closing the valve to aid cleaning of the valve surfaces.

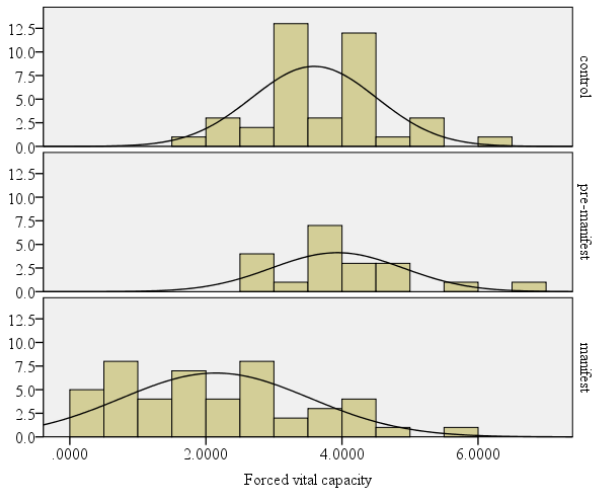
HaB Direct, Northfield Road, Southam, CV47 0RD, Warwickshire, T: 01926 816100

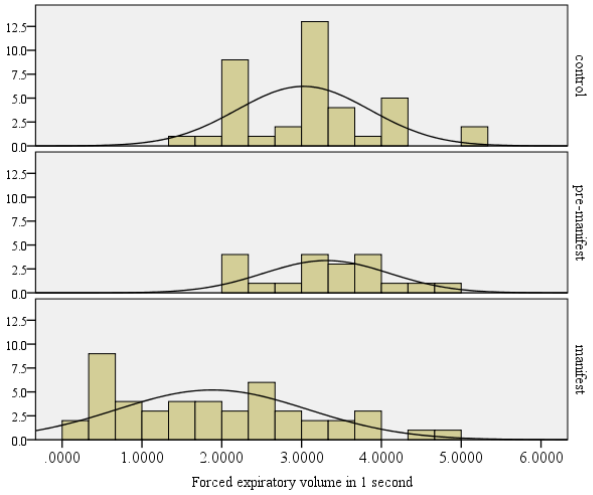
http://www.habdirect.co.uk

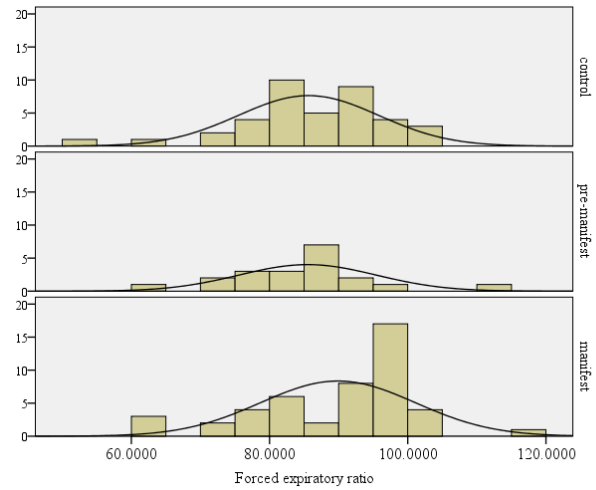
14.5 Appendix 5 Assessment of respiratory function data for normality

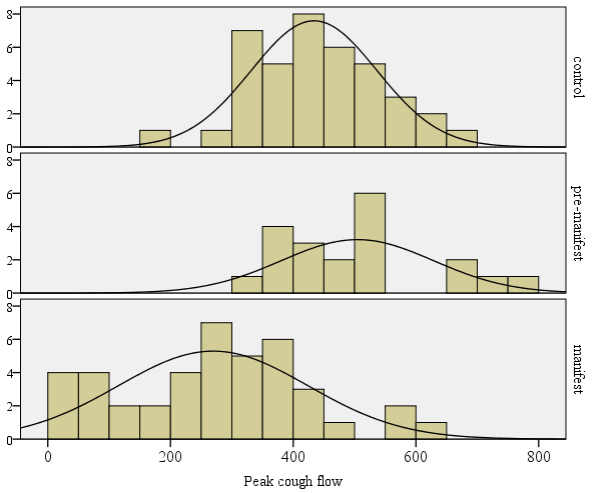
14.5.1 Normal distribution graphs for respiratory function data

a) Forced vital capacity, forced expiratory volume in 1 second, forced expiratory ratio, peak cough flow

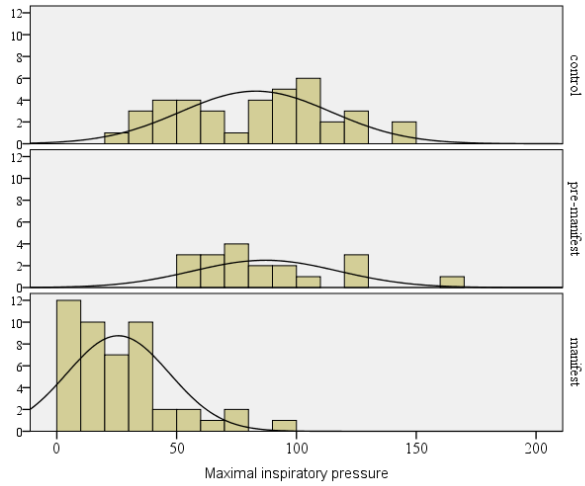


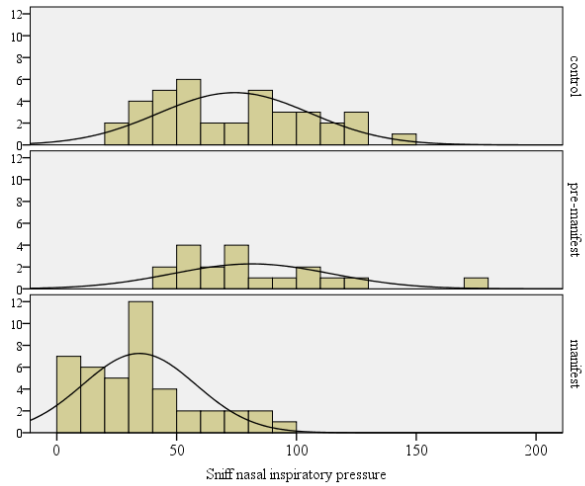


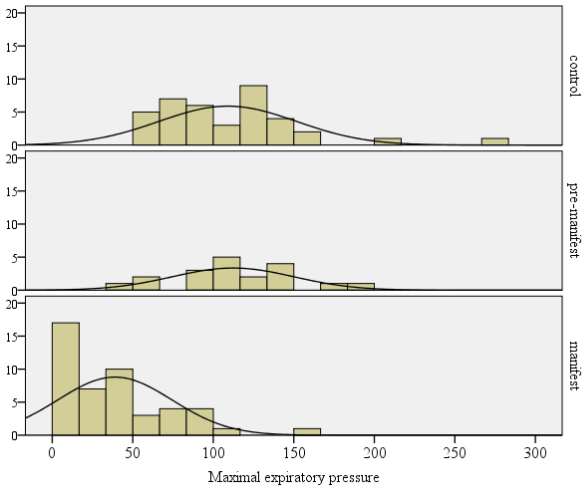


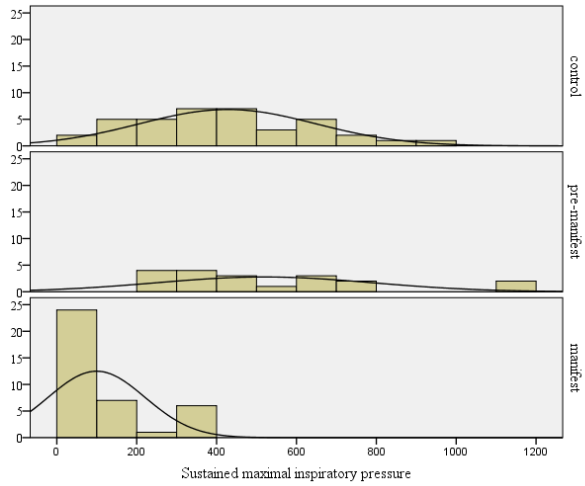


b) Maximal inspiratory pressure, sniff nasal inspiratory pressure, maximal expiratory pressure and sustained maximal inspiratory pressure



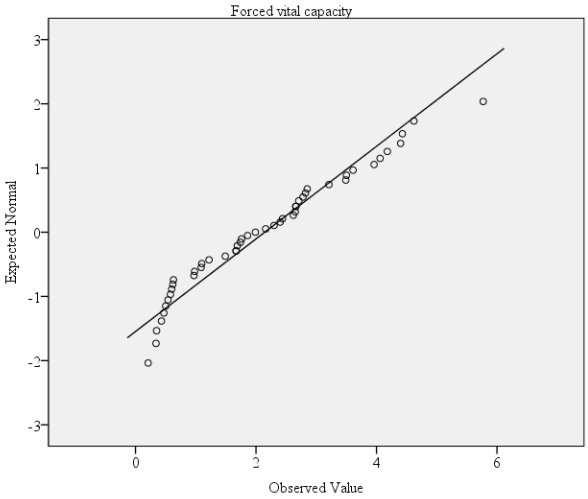


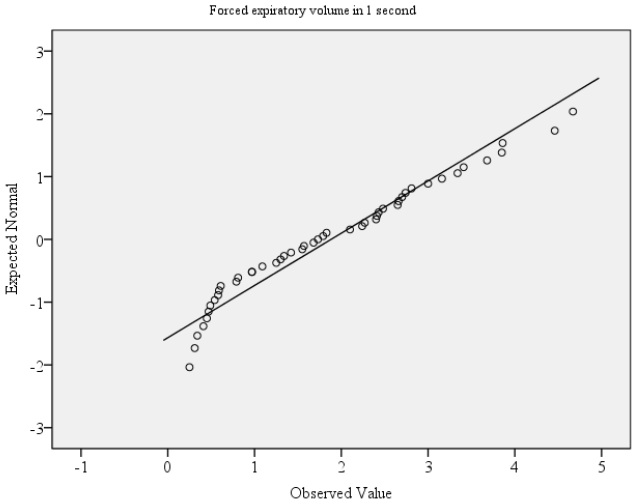


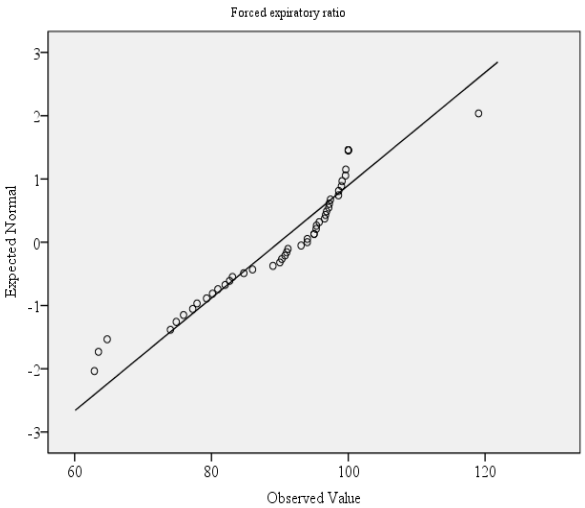


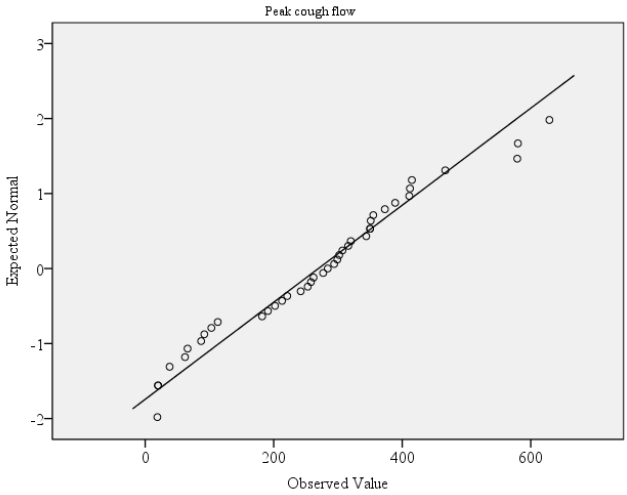
14.5.2 Q-Q plots for respiratory function data in people with manifest HD

a) Forced vital capacity, forced expiratory volume in 1 second, forced expiratory ratio, peak cough flow

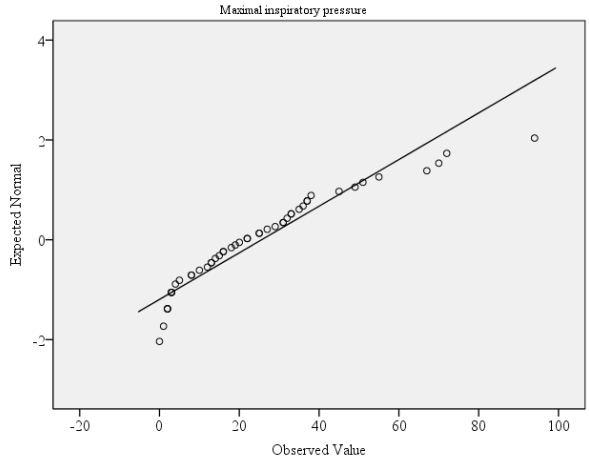


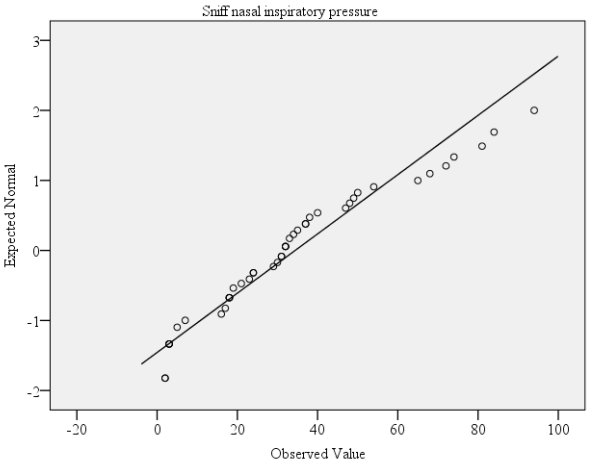


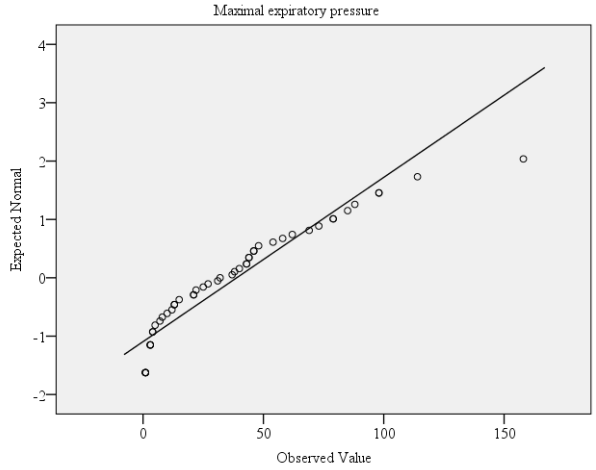


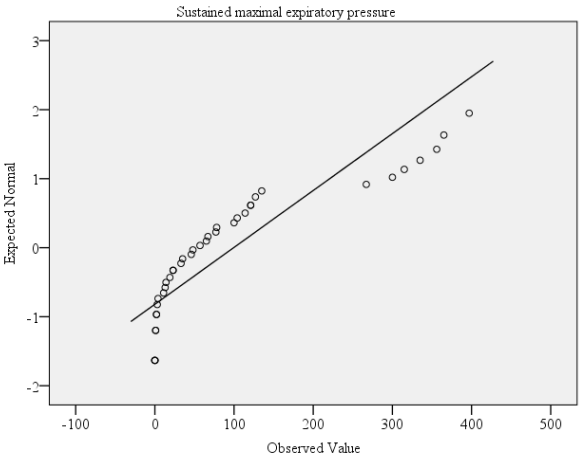


b) Maximal inspiratory pressure, sniff nasal inspiratory pressure, maximal expiratory pressure and sustained maximal inspiratory pressure









14.5.3 Analysis of normal distribution

Shapiro-Wilk and p values and Levene statistic for respiratory function data

	Healthy control	People with pre-manifest HD	People with manifest HD	Levene Statistic
FVC	0.950 p=0.083	0.910 p=0.063	0.948 p=0.036	4.929 p=0.009
FVC% predicted	0.986 p=0.906	0.986 p=0.049	0.943 p=0.024	22.056 p<0.001
FEV_1	0.942 p=0.044	0.953 p=0.411	0.945 p=0.028	6.119 p=0.003
FEV_1% predicted	0.989 p=0.961	0.887 p=0.023	0.940 p=0.017	24.187 p<0.001
PEFR	0.960 p=0.180	0.961 p=0.567	0.938 p=0.014	0.558 p=0.574
PEFR% predicted	0.959 p=0.169	0.895 p=0.033	0.957 p=0.082	4.385 p=0.015
FER	0.943 p=0.046	0.925 p=0.122	0.915 p=0.002	0.730 p=0.485
PCF	0.983 p=0.808	0.956 p=0.473	0.961 p=0.177	2.401 p=0.096
MIP	0.958 p=0.160	0.898 p=0.045	0.904 p=0.001	4.954 p=0.009
MIP% predicted	0.966 p=0.305	0.966 p=0.657	0.894 p=0.001	1.891 p=0.156
SNIP	0.963 p=0.237	0.882 p=0.023	0.937 p=0.022	2.722 p=0.071
SNIP% predicted	0.957 p=0.153	0.946 p=0.332	0.925 p=0.009	1.614 p=0.205
MEP	0.886 p=0.001	0.978 p=0.921	0.896 p=0.001	0.276 p=0.759
MEP% predicted	0.872 p<0.001	0.952 p=0.419	0.859 p<0.001	0.141 p=0.869
SMIP	0.973 p=0.481	0.873 p=0.016	0.769 p<0.001	7.936 p=0.001

Shaded boxes indicate non-normal distribution of data

14.6 Appendix 6 Critical appraisal of literature

Physiotherapy management of respiratory problems in people with neurodegenerative conditions.

Inspiratory muscle training

Summary of critical appraisal of physiotherapy management of respiratory problems in people with neurodegenerative conditions.

	Study design	Focused question	Appropriate design	Population defined	Sample size calculation	Allocation defined	Intervention reproducible	Outcome measures defined	Data analysis defined	Inferential analysis employed	Appropriate interpretation	Generalizability	Clinical relevance discussed
Annane et al	EBR	yes	yes	yes	n/a	n/a	n/a	yes	yes	n/a	yes	yes	yes
Aboussouan et al	Obs P	yes	yes	yes	no	n/a	no	yes	yes	yes	yes	no	yes
Bach	Exp	yes	yes	yes	no	n/a	no	yes	no	yes	yes	no	yes
Bourke et al	Obs P	yes	yes	yes	no	n/a	yes	yes	no	yes	yes	no	yes
Butz et al	Obs P	yes	yes	yes	no	n/a	no	yes	yes	yes	yes	no	yes
Carratu et al	Obs R	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes
Chaisson et al	Exp	yes	yes	yes	no	yes	no	yes	yes	yes	yes	no	yes
Chatwin et al	Exp	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes
Cheah et al	RCT	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	no	yes
Chiara et al	Exp	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes
Fry et al	RCT	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	no	yes
Genç et al	Exp	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes
Gosselink	RCT	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Goldstein et al	Exp	yes	yes	yes	no	n/a	no	yes	yes	yes	yes	no	yes
Inzelberg et al	Exp	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	no	yes
Jackson et al	Obs R	yes	no	yes	no	n/a	no	yes	yes	yes	yes	no	yes
Kleopa et al	Obs R	yes	yes	yes	no	n/a	no	yes	yes	yes	yes	no	yes
Klefbeck & Hamrah	RCT	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	no	yes
Koseoglu et al	Exp	yes	yes	yes	no	n/a	no	yes	yes	yes	yes	no	yes
Lange et al	RCT	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	yes

	Study design	Focused question	Appropriate design	Population defined	Sample size calculation	Allocation defined	Intervention reproducible	Outcome measures defined	Data analysis defined	Inferential analysis employed	Appropriate interpretation	Generalizability	Clinical relevance discussed
Lechtzin et al	Exp	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes
LoCoco et al	Obs P	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes
Mostert Kesselring	Exp	yes	yes	yes	no	yes	no	yes	yes	yes	yes	no	yes
Mustfa et al	Exp	no	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes
Mutluay et al	RCT	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	yes
Nardin et al	Exp	yes	yes	yes	yes	n/a	yes	yes	yes	yes	yes	no	yes
Nauffal et al	Obs (P)	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes
Olgiati et al	Exp	yes	yes	yes	no	n/a	no	yes	no	yes	yes	no	yes
Pfalzer and Fry	Exp	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	no	yes
Pitts et al	Exp	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes
Rampello et al	Exp	yes	yes	yes	no	yes	no	yes	yes	yes	yes	no	yes
Rasova et al	Exp	no	yes	yes	no	yes	no	yes	yes	yes	yes	no	yes
Sancho et al	Exp	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes
Smeltzer et al	RCT	yes	yes	yes	no	yes	no	yes	yes	yes	yes	no	yes
Suleman et al	Exp	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes
Trebbia et al	Exp	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes
Winck et al	Exp	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	yes

Key

EBR	Evidence based review
Exp	Experimental
Obs P	Observational (prospective) study
Obs R	Observational (retrospective) study
RCT	Randomised controlled trial

Critical appraisal of respiratory muscle training studies

Author	Study design	Focused question	Appropriate design	Population defined	Sample size calculation	Allocation defined	Intervention reproducible	Outcome measures defined	Data analysis defined	Inferential analysis employed	Appropriate interpretation	Generalizability	Clinical relevance discussed
Chatham et al 1993	Exp	yes	yes	yes	no	no	yes	yes	yes	yes	yes	no	yes
Downey et al 2007	Exp	yes	yes	yes	no	no	yes	yes	yes	yes	yes	no	no
Edwards et al 2008	Exp	yes	yes	yes	no	no	yes	yes	yes	yes	yes	no	no
Enright et al 2006	Exp	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	no	yes
Enright & Unnithan 2011	Exp	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	no	yes
Inbar et al 2000	Exp	yes	yes	yes	no	no	yes	yes	yes	yes	yes	no	yes
Gossey-Tolfey et al 2010	Exp	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	no	yes
Kellerman et al 2000	Exp	yes	yes	yes	no	n/a	yes	yes	yes	yes	Yes	no	yes
Kwok and Jones 2009	Exp	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	no	no
Leith & Bradley 1976	Exp	yes	yes	yes	no	no	no	yes	yes	yes	yes	no	yes
Mickleborough et al 2010	Exp	yes	yes	yes	no	no	yes	yes	yes	yes	yes	no	no
Romer et al 2000a	Exp	yes	yes	yes	no	no	yes	yes	yes	yes	yes	no	yes
Romer et al 2002b	Exp	yes	yes	yes	no	no	yes	yes	yes	yes	yes	no	yes
Romer & McConnell 2003	Exp	yes	yes	yes	no	no	yes	yes	yes	yes	yes	no	no
Suzuki et al 1993	Exp	yes	yes	yes	no	no	no	yes	yes	yes	yes	no	no
Tzelepis et al 1994a	Exp	yes	yes	yes	no	no	no	yes	yes	yes	yes	no	yes
Tzelepis et al 1994b	Exp	yes	yes	yes	no	no	no	yes	yes	yes	yes	no	yes
Volantis et al 2001	Exp	yes	yes	yes	no	no	yes	yes	yes	yes	yes	no	no

Author	Study design	Focused question	Appropriate design	Population defined	Sample size calculation	Allocation defined	Intervention reproducible	Outcome measures defined	Data analysis defined	Inferential analysis employed	Appropriate interpretation	Generalisability	Clinical relevance discussed
Williams et al 2002	Exp	yes	yes	yes	no	n/a	yes	yes	yes	yes	yes	no	no
Witt et al 2007	Exp	yes	yes	yes	no	no	yes	yes	yes	yes	yes	no	yes

Critical appraisal of systematic reviews

Author and topic	Focused question	Appropriate search strategy	Appropriate inclusion/exclusion criteria	Appropriate system of review	Homogenous results
Geddes et al 2005 COPD	yes	Limited to MEDLINE and CINAHL	Limited to English language	Limited to descriptive analysis	Yes: For targeted inspiratory resistive or threshold IMT vs. sham IMT in MIP, inspiratory muscle endurance, inspiratory threshold loading, exercise capacity, Borg scale, Transitional dyspnoea index No: For targeted inspiratory resistive or threshold IMT vs. sham IMT in 6MWD, work rate, FVC, FEV_1 For targeted inspiratory resistive IMT vs. no intervention in MIP For targeted inspiratory resistive or threshold IMT vs. no intervention in MIP For non-targeted inspiratory resistive IMT vs. sham in MIP
Geddes et al 2008 COPD	yes	Limited to MEDLINE and CINAHL and EMBASE	Limited to English language	Limited to descriptive analysis	Targeted inspiratory resistive or threshold IMT vs. sham Yes, MIP, MIP %predicted, Inspiratory muscle endurance, VO_{2max}, Borg scale, work rate, TDI No PEFR, MVV, Ve_{max}, 6MWD, HRQoL
Gosselink et al 2011 COPD	yes	yes	yes	yes	Yes: MIP, respiratory muscle endurance, 6MWD, 12MWD, Borg, HRQoL No: TDI, CRQ dyspnoea score
HajGhanbari et al 2013	yes	yes	yes	yes	Yes: exercise endurance time; speed of performance; MIP; MVV; respiratory endurance time No: time trials of sports performance; RPE
Houston et al 2008 Cystic Fibrosis	yes	yes	yes	yes	Lack of comparability of methods lead to inability to pool results
Illi et al. 2012 Healthy subjects	yes	Limited to MEDLINE and CINAHL and EMBASE	yes	yes	Moderate heterogeneity in studies chosen for meta-analysis
Ram et al Asthma	yes	yes	yes	yes	No: MIP Heterogeneity not tested on all outcomes due to limited number of studies
Reid et al Cystic fibrosis	yes	Limited to MEDLINE and CINAHL and EMBASE	Limited to English language	yes	Only 2 studies reviewed

14.7 Appendix 7 Interview schedule for intervention study

Interview questions and probes/prompts

1 Did you use the breathing device?

- How often per day and per week?

If Q1 answer is yes then:

2 Was the intensity and frequency acceptable?

- how would you feel if the intensity/frequency was higher/more?
- how would you feel if the intensity/frequency was lower/less?

3. What made it possible for you to carry out the training?

- What difficulties did you have and how did you manage these?
- Where the number of home visits/phone calls appropriate?

4. Did you feel any benefit from doing the training?

- What did the change mean for you?
- Was cough/swallow/speech any different?

If Q1 answer is no then:

5. What made it difficult for you to carry out the training?

- The device technology
- Remembering to do it
- Difficulty of task
- support

General questions

6. What did you like/dislike about the device?

7. What did you like/dislike about the training programme?

8. How could the device/training programme be improved?

14.8 Appendix 8 Transcripts of interviews

14.8.1 Subject01

P=Patient (name changed) C=Wife/Carer I=Interviewer

I: So I'm going to ask both of you, okay about how did you get on in terms of the training, but just as a start because I don't know anything about what you have done.

C: No, alright

I: So just for the start okay I just want to know if Sam has been using the device or not?

C: Yes

I: Yes so he has been using the device

C: twice a day

I: Twice a day and was that for every day during the last 6 weeks?

C: Only once or twice we forgot and I've written on the diary. There were different reasons that is was forgotten but on the whole it's been…

I: So it has been for the majority, for the majority of the days it was every day for six weeks. So that's pretty good, that's good. Now what would you tell Sam how you have been using the device?

P: Good

C: How have you been using it, what do you mean by how?

*dog interrupts dialogue

C: So how do you mean how has he been using it?

I: So for example would we need you to be with him every time?

C: Oh I see, Well what I do in the morning is I put the device together with the mouth piece.

I: Yes

C: And then I leave him to have his breakfast and when he's had his breakfast I say "Go and do your breathing" because I'm out with the dog

I: yeah

C: So when I come back he's done his breathing and then I wash the mouth piece and sterilise it or whatever

I: Okay

C: Erm and then in the evening usually I'm here when he does it. So he does it, you know and I say "Do your breathing" and I'm usually here with him

I: Your with him, so you watch him?

C: Yes

I: So was it easy for you to use the device, was it difficult? What did you think about it?

C: *to pt* What did you think about it? Easy or difficult?

P: Quite easy

I: Quite easy, so in terms of the resistance because I know that the device gives you sort of resistance. So you think that was okay for you?

C: *to pt* do you feel you had to blow hard or was it ok?

P: No it was ok

I: So it was okay, what do you think about if it goes higher, do you think that you would still be able to use it, if we make it harder for you?

P: *grunting noises*

I: Or you don't know, or you cannot tell?

C: Difficult to say

I: Difficult to say, okay

C: I'm not sure if he has done it correctly all the time because I know that when Una has downloaded some of it there has only been so many ways he's done it every day for two weeks and there should be fourteen and the recordings on there, there might only be ten or something. So I'm not sure whether he is doing it properly anyway you know?

I: Ah, so this is one of the things you are not sure okay, So he's trying to use but..

C: He's doing what he thinks yes

I: But you are not sure if he was doing the right thing?

C: because there was no way of knowing because I asked him a couple of times to let me see the screen but it went blank

I: The screen went to blank?

C: The screen goes blank, it doesn't tell him how many breaths you know?

I: And it doesn't show you any diagram or anything?

C: No

I: Would you thing that something set in to the device to show you how you breathe would help you?

C: Yes I think if it came up with the number of breaths that it had actually recorded would be useful

I: Or how hard you are trying?

C: Yes

I: That's just a visual kind of thing that something would help you to make sure you are doing the right thing?

C: Yes

P: Should it go blank?

I: Sorry?

C: Should it go blank?

C: *to pt* Hannan doesn't know

I: Yes so this is why I am asking okay.

C: *to pt* She needs to sort of ask about the machine

P:?11:37?

I: But sometimes, was that a lot of the times?

C: Well, every time I asked him for me to look at it to see how many breaths. To make sure he had done the thirty breaths, it had gone blank.

I: It had gone blank?

C: Yes, I mean when you first put it on you get the picture of the training lungs, the picture of the person with the lungs

I: Yeah

C: and thirty but that's it then, that stays for a little while and then that goes off when he starts using it

I: Oh

C: So at the end I have said to him, bring me the machine and I can see if you have done thirty but there was nothing on there to see them and I wasn't sure to find out how many breaths.

I: Ok, now in terms of the number of times during the day. Do you think two times a day is something acceptable or do you think that if it goes to lower than that would be better?

C: Erm, well twice a day is fine I think, as I say I just put it ready for him and he uses it so

I: So you think twice a day is something that people can work around?

C: Yeah I think so, I think twice a day is acceptable

I: What if it goes to more than that?

C: Oh no, I don't think he would want more than that. He's too tired and you just couldn't fit it in. I'm quite busy so I wouldn't be able to…he can't put it together, I have to put it together for him

I: So it takes time?

C: yeah it takes a little bit of time

I: And it becomes part of the routine that you need to do

C: Yeah well I got into a routine with it now and I think if it was more than twice I couldn't possibly do it

I: Good to know that. Now so we have asked about difficulties now we would like to know what do you think made it possible for you to do it. Because you have done it, you have tried to do it twice a day. Every day for the last six weeks. Which is very good. What do you think made it possible for you to do it? To adhere to it? To comply?

C: Well because we tend to be that sort of people, if we say yes we're going to try and do something. We try to do it, you know? We have been able to fit it in as best we can so you know I mean Sam is here, he isn't doing a lot so he can do it. It's not a problem

I: And he doesn't mind that?

C: No he doesn't mind doing that at all, do you?

P: No

I: He needs you for that?

C: But he does need me to just set it up for him

I: Would he remind you about it or you need to remind him?

C: No, no. A couple of times when I have forgotten for different reasons he hasn't remembered so, so it's me that says do your training

I: So it's you that ??

C: Yes, yes

I: Now did you feel any benefit out of what you have been doing? Have you noticed any changes?

C: No, I don't think so no

I: Nothing in term of the careful speech in particular?

C: His speech is worse if anything, it's not better. His speech has gone down a lot. His breathing, obviously because he had…he was getting very breathless but then he had pneumonia. He was ill, he's not getting breathless anymore but I think it's because he's not ill. Not because he has had that machine, you know I don't think that's done…he seems to be able to walk a bit further. Don't you? But that I think is because he is well

I: Ok so he was ill and he is recovering. So you don't think this is anything to do with the device?

C: No it's a bit difficult to say but I don't think so.

P: I can walk couple miles, two three miles.

C: Okay Sam

I: What is it?

pause

I: Can you talk about what you like in general about the device in particular?

C: It's easy to use I suppose isn't it?

P: Yes

C: Small, easy to use. It doesn't take up any space.

I: Anything that you dislike bout it? That you hate?

C: Only when I said about I think it would be beneficial to show the number

I: To show them the number to give them feedback about what they are doing?

C: Yes

I: I agree with you, this is a good point to have.

C: As there is a screen and there is a picture I am surprised that it doesn't show you how many breaths you are doing

P: Screen goes blank

C: Yes that's what we are saying

I: Yes it does go blank. Anything that you liked about involvement in the study in general? Not about the device.

C: Well we like to get involved. He's happy to do any sort of studies that come up then because we have done the breathing with you in the Heath. It seems a logical follow on from that so…and if it's going to help then anything's worth trying really

I: That's good, anything you dislike about it?

C: No not really

I: Any general comments that you think we need to consider? In future work that may make this work better?

C: No

I: Or make things just get improved

C: As I say, I think it has been quite satisfactory for us. It's only the fact that I think it would help if we could see, because as I say I thought he was doing it. When Una came originally I missed her demonstration of it so I wasn't sure if I was supposed to be hearing or seeing something. So of course when she said that after the first fortnight there were only so many recordings on it, I said he has been doing it twice a day. I just couldn't understand it but I said I wasn't sure how it was supposed to work anyway. She said it should beep. So I don't know, I really don't know

I: Yeah ‘cos this was good that you mentioned this because I was going to ask you this and I forgot about it. I was going to ask you about the home visits that all of us did and also the phone calls.
C: Yeah that’s fine, it’s good to see somebody and you can give them the feedback and they can pass that feedback on to you
I: But you think if you had been here for the first visit…
C: It was my fault I wasn’t here
I: That’s fine, we just wanted to know just to make sure how we can make this better
C: I think because I cannot sit here while he does it because I’m usually doing something else it would be good to be able to visually see that he had done the thirty breaths on the screen. That would be fairly useful. Because I could check it then after each time.
I: But the thing about the breaths it’s probably also about something that, he is probably trying but the machine doesn’t get it.
C: Yes
I: So we are not sure okay, so this is about exploring how the machine is recording and how the things work
C: Yes
I: Okay it may be not his fault that maybe he really tries that thirty times or whatever but it may be the technicality of the machine itself that it doesn’t pick up sometime or it only picks up at a certain threshold even though you are trying.
C: I realise that. Perhaps he wasn’t strong enough, you know he was quite weak
I: When he tries?
C: Yes
I: Now in terms of the phone calls how do you feel about that?
C Yes its fine, you ring up and ask if everything is okay. That’s good, I can then..if I’m having a problem I can say something but no its been absolutely fine.
I: Was that every week?
C: Every other week because Una came every other week
I: Okay so she comes one week and then phones the next week
C: Yes
I: Do you think that is too much?
C: No its fine. To speak to somebody just once a week is good
I: Just to make sure that you are on the track

C: She doesn’t have to do three home visits really, I mean she could just do one at the beginning and one at the end. If she can but I think she needed to come to download the data from the machine

I: But other than that you don’t think she needs to come to demonstrate again or to do something else?

C: No I mean if I had asked her to demonstrate it again I’m sure she would have done but it was my fault, as I say I wasn’t here so I wasn’t quite sure what was supposed to be happening with the machine. So she clarified that so it was alright.

I: I think I have covered most of the questions so anything that you would like to ask me about before we stop recording?

C: No I don’t think so.

I: Any comments that you would like to add Sam?

P: No it’s fine

I: You are okay with that?

P: Yes

I: Okay you are fine for me to stop the recording?

C: Yes

14.8.2 Subject05

P=Patient (name changed) C=Wife/Carer I=Interviewer

I: So what we are going to do today is just ask a few questions about you have been doing during the last few weeks in terms of the breathing device that Una has given you. So the first question, did you use the breathing device.
C: The breathing device
P: Yes I'm breathing much better generally, when I go outside it gets worse
C: Yes but when you were using the device…
P: Yes I thought you were on about something else, outside
I: So my question is did you/he use it at all?
C: Yes
I: Yes ok so he used it?
C: Yes
I: Would you be able to tell me how many times during the week you were using the device?
C: Well most days. Except for the days when he was up in Ty-Wan-Allen on Thursday but he used to do it then, he would do it once when he came back home
I: Ok so that was for 8 weeks was it?
C: 6 weeks
I: So for 6 weeks he used the device almost every day apart from some days
C: He was full of cold last week and there were two days he didn't do it for
I: Apart from these two days can you remember any other days that he didn't do it?
C: Perhaps there was once when he was a bit tired but most days he has done it at least once
I: So if he didn't do it once he would do it twice?
C: Yes
I: Now what about the intensity of the breathing that Una has set up for you, was it ok for you or would you prefer it harder? With more resistance or less resistance
C: No I think it was alright, sometimes he was quite good with it but other times he was a bit short. I think it was because he didn't really understand part of it. He'd blow out more than what he'd take in.
I: So you think that this is because he…
C: He couldn't understand what he needed to do
I: Rather than he is not able to do it, is it?
C: Yes

I: Ok so in terms of the resistance that you have been given, you are ok with that?

P: Upstairs

C: Yes it was good

P: The doctor's upstairs

C: Yes but when you were doing the breathing

P: Oh sorry

C: Una, you did it well?

P: Yes

I: Ok so you don't have a problem with that, what do you think if Una gave you more resistance, would you be able to do it?

C: I'm not sure, we could try when she comes up

I: She would be able to try it by you, I'm not sure about this. That's fine. Now can you tell me what made in possible for you to do the training or to use the device.

P: ?3:27?

I: What has made it possible for you, that you were able to use the breathing device. What made it possible for you? What makes it easy for you to do it? You have done it which is good, great so well done for that. What do you think made it good for you that you were able to do it.

C: The breathing apparatus that he's got to test, he's finding it alright.

I: So you find it alright, you find it easy?

P: Yes

I: So you find it easy, that's good. So it's not complicated, it's something that you were able to do easily?

C: Yeah

I: And what else? Did you need to be with him every time he did it?

C: Oh yes I, but he's get on with it but sometimes he would stop and then I'd have to encourage

I: Did he need points?

C: Sometimes, he needed, because he would forget which way he was going (breathing)

I: So in that term ok he needed you to tell him which way to do it?

C: Sometimes I would stand there and go "in, out" and he'd do it perfectly then. Breathe in, breathe out and he'd know which way he was going. But sometimes he'd get a bit lost in that.

I: So you have been sitting beside him every time he has been doing it. Do you think that is you are not there, the situation will be different?

C: Might, perhaps he wouldn't do it, complete it than. I think one of two puffs . Although he would look up but he wouldn't be able to see the number of times that are left for him to do. So I'd tell him you've got so much to do. Keep going, and he would. I think there was only once…no twice I think he didn't complete the thirty breaths

I: That's good, now, did you have any difficulties using the device or any part of the programme?

C: No he was alright

I: Yep, So you wouldn't say there are any difficulties using the device? It's not too technical, stopped working sometimes? You couldn't program it well or?

C: No nothing

I: So what do you think about the home visits that Una has provided? Do you think it is important?

C: They were good, important to see that he was progressing, doing it properly

I: What about the phone calls from Una

C: Yes Una rang to see if he had completed the sessions, good to know that you were keeping in touch to see that everything was progressing. I think, if you didn't we perhaps would be prone to not do it she is going to phone, I had better do it.

I: Just going back to the exercise, did you need to remind him to do the exercises?

C: I'd have to remind him every time

I: Now, did you feel any benefit or changes?

C: Yes, he told the nurses that he feels a lot better. going up the stairs – finds it easier.

I: Anything else, what about cough or his speech?

C: No nothing

I: Would you be able to tell me things that you most liked or disliked about the device?

C: Quite easy to use, once Una told us how to use it,

I: Was there anything you didn't like about the device

P: Found it easier to breathe out rather than breathe in

I: Is there anything else that could make it better

C: No

I: Great thank you, I am going to stop it here.

14.8.3 Subject08

P=Patient (name changed) C=Wife/Carer (name changed) I=Interviewer

I: Ok so the machine is recording now, so for the next 10 minutes or so we will just talk about the study that you are just finishing. Erm and eh I have got a list of different questions to ask you about that em and I wanted to say em if your wife wants to add anything or has anything to comment on em I think it would be really useful and helpful because what we need to understand is whether this is useful if the programme itself makes sense or there are things that we can do differently if you think it is worth doing erm just to start off Did you use the breathing device?

S: Yeah

I: Yes

S: Ye

I: And and did you use it every day?

S: yeah

I: Yes, ok. Em and how or how often during the day do you use it?

S2: Twice a day

I: Twice a day ok, so and how did you feel about doing it twice a day was that too much or too little or was that easy for you to do?

S2: It was Ok most days just em certain days when he was doing something he may only get to do it the once, I have written that down.

I: And that's all in the diary anyway

S2: Yeah he may only get to do it once like in the mornings and a better routine otherwise and then later on if we went out he would find it difficult fitting that in

I: Yeah cos even though

S2: Cos if it's, with Clive it's, em for the pm one, it's got to be before 7 o'clockish, cos from 7 o'clock onwards, he gets really tired and I just found that there's no point in doing in it

I: No point … and it's not.. even though its portable it's not the sort of thing that you can take out with you

S2: No not really

I: No

S2: It's not the type of thing you take it if you're out for a meal or something

I: No (laughs) you can't sit there and do it

S2: No

I: So it's easy for you to use in the home

S2: Yeah

I: But it's not something you would take out

S2: Neh

I: OK so if you were busy during a day then you would tend to so it in the morning and then leave it S2 mm

I: Ok, and about, in terms of em em doing it every day / would you say that you managed to do it every day?

S: Yea

S2: Managed to do it most days and like I said, he definitely did the morning one it was only if we were doing something

I: Ok

S2: Because in the period of time that Clive has had it, we have had half term so we've been busy with trips and things

I: Yeah, Ok all right so how would you feel if we said to you well you only need to do it twice a week do you think that would be better or do you think doing it every day is good as part of the routine or

S2: em well definitely for us the morning is part of a routine so that wouldn't be a…

I: Wouldn't be a problem

S2: No

I: So doing it every day is fine

S2: Yeah

I: As long as it's in the morning

S2: Yeah, like I said with Clive he gets tired towards .. and if I miss that because I'm doing something then I know there's not much point because he won't actually do it like he's supposed to take in the deep breaths

I: Ok

S2: Because he is so tired

I: Right so so really for it to be a good session would you say that you need to be helping with it?

S2: yeah definitely

I: Ok

S2: Yeah coaching him

I: For coaching Ok, alright, so some of the questions, Clive I am going to ask Sally really about what was and what was not good

(S and C laugh)

I: Because, so coaching and having you there to coach is an important part of that

S2: Yes, I would say yes

I: In terms of the prompts

S2: Yeah

I: Ok… em so what do you think was difficult about using the machine, was there anything particularly difficult or did you find it self-explanatory?

S: No eh no

I: Its quite easy isn't it?

S2: Yeah

I: Just press a button

S: Ye

I: A bit like the Dictaphone em … ok so you didn't have any problems with the device itself and in terms of the amount of times that Una came to visit em and phone in terms of the support if you had any questions, was that appropriate or

S2: Yeah

I: It wasn't too much

S2: No

I: No and you didn't need any more?

S2: No

I: So it was just the right balance?

S2: Yes

I: Ok alright em did you feel that the training helped you? Do you think it's made a difference to you?

(S laughs)

S2: I wouldn't have said so, do you feel any different Clive?

S: No

S2: Not really no

S: No

I: No OK alright em so is there anything different about your speech at all? Do you think his speech is any different? No? And what about swallowing?

S: em ok swallowing

S2: Maybe, maybe the swallowing yeah maybe, cos you haven't bitten your lip or anything have you

S: No

I: So that's healed nicely, so you used to bit your lip

S: Yeah

I: And do you know why it was that you bit your lip?

S2: It was just when he was eating

I: Ok and you haven't been biting your lip as much

S: No

I: Can you think about how long that's been?

S2: Well that was before he started, he hasn't been biting his lip for quite a while that's' a long time

I: Longer than the intervention

S2: Yeah I would say yeah

I: So it's not the breathing device then

S2: No, the only thing that I would say is that he seems to be eating quicker

I: Ok so the time that it takes to get the food off the plate

S2: Down yeah

I: Ok

S2: Fast

S: Um um

I: So quicker swallowing then

S2: Yeah

I: No choking

S2: Well he still gets episodes of choking

S: Yeah

I: But no em I guess what I am saying is that the quicker might not be safer

S2: No

I: So is the quicker also as safe as it was before ..

S2: Yeah

I: So there's no more choking

S2: No

I: No, alright OK em so you just in general then what did you was there anything you particularly like about doing the training

S: Eh yeah

I: Yeah?

S: Ye

I: What did you like about it?

S: (not understandable)

I: Did you like practicing the breathing?

S: Yeah

I: Is there anything that you don't like about it?

S: No

I: No?

S: No (laughs)

I: Ok are you going to carry on doing it

S: (not understandable)

S2: We haven't really thought about it have we? Cos we get to keep it

I: Yes you get to keep it yeah, you can keep it em

S2: Maybe we might not do it twice a day maybe as part of the em when he wakes up he is expecting to do it

I: Yeah

S2: Perhaps we'll do it as much as we can Clive?

S: Yeah

I: It's not a difficult thing to do, is it?

S2: No

I: Cos it's very contained, how long does it take you to do one session?

S2: Not long, in the mornings its quite quick a few minutes, then it's done in'it

S: Yeah

S2: Doesn't take long at all

I: Not long at all

S2: No

I: So in comparison to the other exercise programmes this is a really easy thing to do (laughs) OK

S2: Plus obviously we're at home

I: Yeah, it does help being able to do it at home and fit it into your routine. Is there anything else you would like to talk about, about this study? And sort of your experience of doing it? Anything else that you want to let us know?

S2: No - has it been found to be beneficial at all?

I: We don't know,

S2: You don't know

I: We don't know em this this study is very much about em seeing what people thing and seeing whether people can do it and fit it into their lives and em it's only 2 thirds of the way through so em

S2: So what is the thinking behind it?

I: The thinking behind it is that if you can em increase the strength of the breathing muscle that it can help both with just breathing and coughing so if you do have a problem were you swallow food

S2: Yeah

I: You've got then a good cough and because if you have these muscles that are strong then the cough is good and can prevent the food going the wrong way so it's as a long term precaution the theory is that if we keep these muscles as strong as possible that you would prevent chest infections. That's the one theory. The other theory is that if your breathing muscles are strong em then the work of breathing takes less effort and that means that you can concentrate more on your walking and other muscles so there is some kind of thoughts but none of it is proven that if you can keep these muscles ….so if you can.. this is mostly used by athletes

S2: Yeah

I: To strengthen the breathing muscles so that they can then have less work on their breathing and more energy and more effort going into their running muscles and walking muscles so em that's really the 2 kind of thoughts about it em so certainly what would happen is a soon as the analysis is done, Una will get back and tell you what has happened and that has changed. And she will be discussing that with you and she can look at the individual data and say whether there has been any changes and I suspect that that would help you make a decision

S2: Yeah

I: About whether you carry on. I think that's the feeling OK

S: Ye

I: So you've got an appointment so what I will do then is, I am going to turn that off.

14.8.4 Subject11

P=Patient (name changed) C=Wife/Carer I=Interviewer

I: Okay, so thank you for taking part in Una's research, it's just a few questions to go through now about the intervention em so I'll just start the questions, the first one is Did you use the breathing device?

S: Yes

I: Ok and how often per day and per week

S: Ehm we were supposed to use it twice ehm we tried as often as possible to do it twice ehm it wasn't always possible ehm just simply because David was having problems and I think it was also getting used to the apparatus, because we had a few difficulties with it

I: Ok, so was the intensity and frequency acceptable?

S: Yes, yes

I: How would you feel if the intensity and frequency was higher or more?

S: eh it would have been … a bit harder if it was higher, simply to get it all done in amongst all the other things as well (laughs)

I: How about if the intensity or frequency was lower or less?

S: Eh it would obviously be easier ehm but ehm we felt that about once a day would probably be Ok rather than twice.

I: Ok ehm and what made it possible for you to carry out the training?

S: ehm well I think it was the fact that…. we were always here with David anyway, so it made it easier because if we weren't here it would have to organised with a carer or something or somebody else to do it.

I: Ok ehm what difficulties did you have, if any, and how did you manage them?

S: Eh, the biggest difficulty we had was with the mouthpiece because with the Huntington's the muscle co-ordination is quite complicated to get the mouthpiece in and to get David to seal around the bit. In fact it was so difficult that the only way we managed to do it was at first to take the mouthpiece off completely so David was just blowing straight into the apparatus

I: Right

S: Uhm but eh Una felt that perhaps we weren't getting the right distance from the apparatus so she allowed me to cut the mouthpiece off so that David could slip the tube straight into his mouth without the … the snorkel type mouthpiece which requires the mouthpiece to go

behind the gums and then for the teeth to bite on to the little eh lugs that were there, but that was far too complicated. It was made a lot easier by cutting the ends of the mouthpiece off.
I: Ehm were the number of home visits and phone calls appropriate?
S: Yes, yes, Una was phoning me weekly to see how we were getting on and em that's where she was advising me well cut the tube and
I: Right
S: And see how we get on that way, rather than not being able to do it all because when we had the mouthpiece as it was supplied it was virtually impossible for David to do one exercise successfully
I: Right so having that extra input was quite helpful
S: Yes, yeah yeah
I: Em did you feel any benefit from the training?
S: Em it's hard to tell if there is any benefit in other words the strength of it because we don't know what the results were but eh certainly over a period of time em David was getting the hang of how to breath in cos at first he was doing very short little puffs which weren't successful
I: OK em what did the change mean for you?
S: Em not sure what that means, em it well I don't know (laughs) I really don't know
I: Ok (laugh) em so and you have put here the question was cough, speech, swallow any different you're unsure of that, is that right?
S: yeah, yeah we're unsure we don't know really cos there was nothing for us to measure against
I: Ok em what made it difficult for you to carry out the training you've already mentioned the mouthpiece is that the one …
S: Yeah mainly the mouthpiece, we also found that there was a couple of times that the device seemed to jam
I: Right
S: So I was trying to ask .. David was failing to actually do any successful blows , I mean we were trying about 15 times and it was still reading about 30 remaining so it hadn't budged 1 em and then I took off the headpiece and out it back on again and then we tried again em so it seemed to be that it hadn't quite meshed you know onto the head and then the second time part way through the test, the device seemed to have stuck because David ,half way through the test just couldn't get the numbers to drop down any more, so I gave it…. I had to clear it I thought so why isn't it working so I thought well I'll test it and I gave it one good, well I

tried sucking it and I thought my god its impossible I can't even do it so I gave it one good blow and a really hard suck and it seemed to clear it then.
I: Right
S: So it felt like the device had actually stuck
I: Right Ok em anything else about the training that perhaps being able to remember to do it or…
S: Em found that it was easier for David to do it em lying down but in a sitting upright position when he was in bed with the head of the.. the backs of the …back of the bed raised up
I: Right
S: So that he was lying but sitting upright, as it were in bed, that seemed to be easier. I don't know .. do you agree with that Dave? rather than sitting in the chair like this, he seemed to find it better when he was relaxed in bed
I: Right
S: And doing the exercises seemed to be more successful in that position
I: Ok so changing, slight change in posture
S: Yeah so lying down but with his torso slightly raised at 45 degrees seemed to be the ideal position.
I: Ok em is there anything that you liked or disliked about the device apart from the mouth piece?
S: Eh no not really it was quite straightforward to use
I: Ok em any likes or likes about the training programme?
S: No
I: Em how do you think it could be… how could the device or the training programme be improved?
S: Eh well the only improvement would be to have I thought that if there was a more - without the snorkel type mouthpiece em but a more rigid end of the tube or something that fitted over the tube. If something fitted over the tube, that was rigid that David could put into his mouth without any obstruction, in other words just a plain elliptical mouthpiece that was more rigid, cos what was happening sometimes was, David when he had the tube in his mouth to get a firm seal around the mouthpiece em he was actually biting on the tube so that was constricting the flow of air as well so there was quite a combination of things em so if, if the tube how can say – the endpiece that goes into the mouth didn't have all the clutter so that it was just a plain oval tube

I: Yeah

S: But was more rigid that he could get a firm grip on it without actually crushing the end of the mouthpiece

I: Yeah

S: That would have been perfect

I: Ok, that's all the questions thank you very much

S: That's alright Kate

14.8.5 Subject12

P=Patient (name changed) C=Wife/Carer I=Interviewer

I: So we are recording what we are talking about now, so basically I just need to talk to you today about the machine and the exercises. How you did it and what you thought about it. So, I already know that you used, you did use this. On average how many times a day did you do the training.

P: On average I would say I used it twice a day but obviously if I was to average it out it would probably be one and a half/one and three quarters a day

I: There were some things that you didn't do, and what were the reasons for why you didn't do it

P: To start with, I didn't set an alarm properly so that didn't help much. I still manage to sort of squeeze them in. So having an alarm helped but there were still times, especially when I went away for a few days I forgot to take it with me. There were other times when the alarm went and I was busy so I forgot

I: Just about the alarm, did you decide that was the best way to remind yourself

P: Yes I did

I: So you kind of said I'm going to set it. What were the times of the day?

P: There was one at about 11.30 because I normally get up at about 10 so it gives me some time to wake up first and at about 6pm after I take food

I: Ok and was that intensity, so how often you did it and how hard you worked, was that ok for you?

P: Yes that was ok

I: There was just sometimes if you were out or you were busy that you didn't do it but you managed to fit it in

P: Yes that happened sometimes

I: So you definitely did it once a day for the whole time

P: Yes

I: Would you be able to do it more often in a day?

P: Yes I don't see why not, it would be annoying yes. It terms of the physical, being able to do it physically, yes.

I: Its annoying because it interferes with things or?

P: It does, I mean…if it was part of me getting better its worth doing. So therefore from that point of view it would be fine to do it a few times a day if it benefitted me, as a point of view

for the study. For me it is less likely to benefit me at the moment, really because I'm quite early on post….of the whole thing

I: So if you thought that it was helpful then it's ok to do it, but just because you are doing it and you don't really see the point of doing it at this moment.

P: Yes

I: Is that what you mean?

P: Yes

I: So the things that you did to make it possible for you to carry out the training was setting the alarm, what other things did you do?

P: I think that's mostly it, obviously leaving the device somewhere obvious such as in the kitchen so when I popped in for a drink or bite to eat and you see it, that helped.

I: So having visual, not putting it away in a cupboard. That was a conscious thing that you did?

P: To start with it was sort of an accident because I was in the kitchen because I had it washing or drying all the time but afterwards yes it was something I did.

I: Were there any problems or difficulties that you had with doing or using it

P: Not really, I did lose the end which wasn't particularly clever.

I: The mouth piece

P: yes, I have the mouthpiece somewhere but I didn't have any trouble using it as it is

I: So you don't have a mouth piece and it still worked without a mouthpiece, ok. How long into the study do you remember that you lost the mouthpiece.

P: About two thirds of the way it

I: By then you had kind of learnt how to use it, so you just…

P: Yes

I: It terms of the visits, so Una coming to visit you. Was that helpful?

P: Yes I mean it helps to go over what's going on and her turning up to remind you

I: Were there enough visits, do you think there were enough visits? Do you think she could have done more or do you think that she needed to do less?

P: Just fine the way it is to be honest

I: Fine, so it was the perfect balance?

P: Yes

I: And the phone calls?

P: Yes that obviously helps as well, it keeps you motivated and reminds you again.

I: So it's mostly about having a reminder for you?

P: Yes

I: Ok, do you feel any benefit from doing the training?

P: I haven't particularity noticed anything myself, no.

I: So you don't have any difficulties with cough or swallowing problems now

P: No I don't

I: And you haven't noticed anything different

P: No

I: Is there anything you particularly like about the machine?

P: I suppose once you got it going it was very easy to use once it has been set up you turn it on, it's fairly easy to use. That's about it.

I: Anything you don't like?

P: The buttons on there are completely…why do you need to press the on button to go to the menu button and why does the up and down button on the left, why is that a play button? Which makes it seem like it should be that start but not the ? button

I: Oh I see. It should have up and down things for the menus

I: Yes because the button looks as though it is a play button on a video machine

P: So I did that quite a lot

I: So it's not intuitive, the way it looks doesn't work the way you should it should work

P: The charge time is phenomenal. I had to leave it plugged in overnight to get a decent charge on it

I: So you would take it off and it would run down quite quickly?

P: Yeah you know the battery sign, I would leave it in for a few hours and it didn't seem to make a difference

I: Is there anything you particularly liked about doing the program?

P: No not massively

I: Would you say you are impartial?

P: Yes I would say, no comment

I: Are there things you particularly disliked?

P: No massively either, either way for the sort of helping out the study I'm always up for that. From that point of view it was good to do.

I: So you feel that by doing it you can contribute to finding ways to help with the disease and be involved in the research, but you didn't feel it particularly relevant to you

P: No, I'm assuming from my point of view I'm a baseline

I: So what do you think should be done differently, what could be done differently?

P: Apart from the problems with the thing itself it's fine

I: So you were happy with the amount of support that you had and phone calls, it was fairly easy to fit into your life if you had alarms on your clocks and you left it visible

P: Yes

I: If I summarise, if you thought it would help you would continue to do it?

P: Yes

I: And so we just have to wait and see, ok well I think that is all. Is there anything else that you wanted to say about this particular study

P: No

14.8.6 Subject13

P=Patient (name changed) C=Wife/Carer I=Interviewer

I: Did you use the breathing device?

P: Yes

I: How often per day and week?

P: twice a day

I: And how often was that? Was that every day or every other day?

P: Every day

I: So you used it twice a day every day?

P: Yes

I: Was the intensity and frequency acceptable? So how often you had to do it?

P: Yes

I: And the intensity, how difficult it was, was that too difficult or ok?

P: Ok

C: It was difficult at one stage but it was on the wrong setting, when the lady came out she looked at it and we realised that's why he was struggling a little bit

I: But apart from that it was alright?

C: Yes

P: Yes

I: How would you feel if it was a bit harder or you had to do it more often? Would you feel happy about that or not so happy?

P: Happy

I: And what if you had to do it less often and it was a bit easier? Or was it just right as it was?

P: Yes

I: What made it possible for you to carry out the training so what helped you to do it? For example, having reminders

P: I just knew

I: So you had good memory?

P: Yes

C: Yes he would remind us!

I: And what about Una phoning you, did you feel like the number of phone calls you were getting was appropriate?

P: I didn't care about them!

I: Did you feel any benefit from doing the training

P: Yes

I: In what way? Did you find your coughing was any different or swallowing?

P: Swallowing is a lot better

I: So did that make anything easier for you? Did that change mean anything to you? Did it help when you were eating?

P: Yes

I: So you didn't have any difficulties with it?

P: No

I: What did you like or dislike about the device

P: Nothing

I: Nothing you liked or disliked?

P: No

C: At the start we found with the plastic gum shield we couldn't manage it with that on and just did it directly because it kept falling off. It was easier not to use it

I: What about the training programme, was there anything you liked or didn't like

P: I liked it

I: What did you like about it?

P: For the future

I: for the future? You thought it might help for the future? Is that right?

P: Yes

I: Do you think it could be improved in anyway like you said you took the shield off to make it easier, is there any other way you would improve it or the training programme itself?

P: It's alright

I: What about the size of it, was it easy to handle?

P: Yes

C: I think it was easy to handle but I'm not sure if he would managed to get it on and off himself, I think he would need someone independent to do that, like switching it on and loading it. We only managed to drop it once!

I: That's all the questions, thank you very much

14.8.7 Subject14

P=Patient (name changed) C=Wife/Carer I=Interviewer

I: Did you use it, the breathing device?

P: Yep

I: How often per day

P: Twice a day, sometimes three times

I: Was that every day?

P: Yes

I: Was the intensity and the frequency acceptable

P: Yes

I: How would you feel if it was higher? If it was a bit harder or you had to do it more often

P: I would have done it the same

I: Or if it was less difficult, how would you find it?

P: I was happy the way it was

I: What made it possible for you to carry out the training?

P: Nothing, I just had to get on with it

I: Were there any difficulties you had with doing it?

P: No

I: Were the number of home visits and phone calls you had appropriate

P: Yes

I: Was there anything that helped you to do the training? That you were able to do it three times a day

P: ?

I: Did you feel any benefit from doing the training?

P: No

I: It didn't make any change to you at all?

P: No

I: You didn't notice anything with coughing, speech or swallow?

P: No

I: Did you find actually using it difficult?

P: No

I: Were you able to remember to do it or did you need some reminding or prompting from anybody?

P: No I reminded myself

I: And you didn't find it difficult as you said?

P: I kept the device in view otherwise I think I would have forgotten it

I: You kept it in view so you could see it and that's what helped you?

P: Yes

I: Was there anything you didn't like about it?

P: No

I: Was there anything you didn't like or did like about the training programme

P: No?

I: Anyway you think it could be improved?

P: How do you mean?

I: The way you use the device or was the mouthpiece okay to use?

P: Yes

I: Do you think the size of it was ok?

P: Tidy

I: It was okay to hold and use it?

P: Yes

I: Well that's it then, thank you very much

14.8.8 Subject 17

interview notes

1 Did you use the breathing device? Yes

- How often per day and per week? Twice a day every day, morning and afternoon

If Q1 answer is yes then:

2 Was the intensity and frequency acceptable? Yes

- how would you feel if the intensity/frequency was higher/more? Would be difficult to fit in if more often.
- how would you feel if the intensity/frequency was lower/less? Would be ok

3. What made it possible for you to carry out the training? Wife reminded participant to do the training

- What difficulties did you have and how did you manage these? Difficult to use in the afternoon, the device seemed to not work properly
- Where the number of home visits/phone calls appropriate? Yes, just right

4. Did you feel any benefit from doing the training? No

- What did the change mean for you?
- Was cough, speech, swallow any different?

If Q1 answer is no then:

5. What made it difficult for you to carry out the training?

- The device technology – easy to hold, good size
- Remembering to do it – reminders from wife
- Difficulty of task –not difficult
- support

General questions

6. What did you like/dislike about the device? Nothing disliked, size of it made it easy to use

7. What did you like/dislike about the training programme? No comments

8. How could the device/training programme be improved? Couldn't suggest any way of improving it

14.9 Appendix 9 Publications

14.9.1 Jones et al 2011

RELIABILITY OF DIGITAL ANALYSIS OF THORACIC, NECK ANGLE AND HEAD TILT MEASUREMENTS

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Abstract

Background: Postural re-training is one element used in the physiotherapeutic management of spinal disorders. Clinicians need outcome measures that are accurate, reliable and easy to use to monitor effects of treatment and to provide justification for the management of these conditions. This study aimed to assess the reliability of digital video analysis of thoracic, neck and head tilt angles using one measurer within one day.

Methods: Twenty healthy subjects were recruited. L4, C7 spinous processes and tragus were marked on the skin and identified with reflective markers. The subject sat in a relaxed comfortable position in a chair and was video recorded from a lateral view for one minute. The markers were removed and the subject rested, in a chair, for a few minutes. Two further recordings were taken in the same day. Still images were taken at 30seconds of the recording and were analysed using a bespoke programme within MATLAB software. Analysis included Intraclass Correlation Coefficients (ICCs) and Bland Altman plots.

Results: Excellent reliability was ascertained for thoracic, neck and head tilt angles identified by ICC of 0.94 (mean difference 0.34° ±4.7°), 0.91 (mean difference 1.1°±3.7°) 0.84 (mean difference 0.9°±4.9) respectively. All points, except one for neck angle and head tilt angle and two for thoracic angles, were within 95% limits of agreement.

Conclusion: Digital video analysis using MATLAB is a reliable way to measure thoracic, neck and head tilt angles. This is an inexpensive method for measuring posture that could be used in the management of people with spinal disorders.

Conflict of Interest: None

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http://www.bjjprocs.boneandjoint.org.uk/content/93-B/SUPP_IV/490.4.short

14.9.2 Jones et al 2012

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Narrative review

Management of respiratory problems in people with neurodegenerative conditions: a narrative review

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Abstract

Background Respiratory failure and dysfunction are common problems in many neurodegenerative conditions. Although physiotherapists manage these problems, it is not known which treatments have been studied and their efficacy.

Objective To review evidence on the management of respiratory problems in people with neurodegenerative conditions using the PRISMA approach.

Data sources Comprehensive searches were conducted using the following electronic databases from inception to May 2010: HUGEnet, SIGLE, British Library Direct, CINAHL, Medline, AMED and Web of Knowledge. Bibliographies of all studies and systematic reviews were searched by hand.

Study selection Studies were selected based on: self-ventilating participants with neurodegenerative conditions; interventions aimed at improving respiratory function; and any valid and reliable measures of respiratory function as outcomes.

Study appraisal Studies were appraised by one reviewer using the Critical Appraisal Skills Programme. Data were synthesised using a narrative approach.

Results Thirty-five studies were included in the review. The strongest evidence was for the use of non-invasive ventilation for people with amyotrophic lateral sclerosis, although this was weak. The evidence for the use of respiratory muscle training and methods to increase peak cough flow showed a positive effect, but was also weak.

Conclusion There is weak evidence for the positive effects of physiotherapeutic interventions for respiratory problems in people with neurodegenerative conditions. Further work is necessary in specific neurodegenerative conditions to identify why respiratory problems occur, and larger scale studies should be undertaken to investigate management of these problems.

Keywords: Neurodegenerative conditions; Respiratory insufficiency; Physiotherapy

Introduction

Rationale

Respiratory dysfunction is common in neurodegenerative conditions, such as multiple sclerosis [1], amyotrophic lateral sclerosis (ALS) [2] and Huntington's disease [3]. Physiotherapeutic management of respiratory problems is often supportive rather than preventative, only taking place in the middle and late stages of the condition [4]. With the exception of national guidelines for the use of non-invasive ventilation in patients with motor neurone disease [5], there are no national guidelines for the management of respiratory problems in people with Parkinson's disease, Huntington's disease or multiple sclerosis. The British Thoracic Society/Association of Chartered Physiotherapists in Respiratory Care guidelines for the adult, spontaneously breathing patient [6] focus on people with neuromuscular disease but do not provide sufficient detail for neurodegenerative conditions. Neurodegenerative conditions differ from neuromuscular diseases in that the former refers to central neurological disorders, and the latter refers to post-neuromuscular junction disorders. Multiple sclerosis, Parkinson's disease, Huntington's disease and ALS/motor neurone disease are neurodegenerative conditions with central nervous system processing problems and peripheral weakness.

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14.9.3 Jones et al 2013

Reliability and validity of peak cough flow measured via face mask

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Background

Measurement of peak cough flow (PCF) is integral to assessment of patients with neurodegenerative conditions to determine use of assisted cough strategies. The manoeuvre can be performed through mouthpiece or face mask, yet there is no evidence for the reliability or validity of the measure. The aim of this study was to determine the reliability and validity of measuring PCF via face mask in a healthy population.

Method

Study design was within-day intra-tester reliability, and validity was assessed by comparing facemask with mouthpiece measurements. 23 subjects were recruited from Cardiff University. Subjects performed 3 PCF (face mask) and 1 PCF (mouthpiece) measurements in one day in a laboratory. Each measurement was the highest of 3 manoeuvres. Reliability was assessed by intraclass correlation (ICC) and limits of agreement (LOA); validity by Pearson correlation coefficient and LOA.

Results

Within-day intra-tester reliability had excellent reliability, ICC=0.931. Mean difference between first and third measures was -4.09 L/min, 95% LOA were 62.12, -70.30 L/min. The relationship between PCF (face mask) and PCF (mouthpiece) was statistically significant r=0.929, p <0.001. Mean difference between face mask and mouthpiece measurements was 12.17 L/min, 95% LOA were 107, -83.46 L/min.

Conclusions

PCF measured via face mask is a reliable and valid measure in healthy subjects. Although the mean difference between the 2 methods was 12.17 L/min, the broad LOA would suggest the two methods should not be used interchangeably. Further research needs to be carried out to assess reliability in people with neurodegenerative conditions to ensure external validity.