UNIVERSITY OF SOUTHAMPTON

Faculty of Social, Human, and Mathematical Sciences

School of Psychology

Using the methacholine challenge to determine how psychological mechanisms impact asthma symptom perception and quality of life.

by

Hasina Khatun

Thesis for the degree of

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ABSTRACT

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The first chapter of this thesis reviews the literature exploring the association between anxiety and asthma, and the effect this has had on potential outcomes. The following outcomes are affected by the relationship: quality of life, control, symptom perception, dyspnoea, lung function, and healthcare utilisation. 26 studies were identified after searching four distinct specialist databases of publications. Quality of life and control was reduced in asthmatics who reported higher symptoms of anxiety. Reduction in dyspnea (or breathlessness) and symptom perception was lower in anxious groups and not associated with lung function. Finally, the articles highlighted the link between anxious asthmatic and increased healthcare utilisation. Anxiety plausibly has a role in misinterpretation of symptoms, affecting control, subsequent quality of life, and healthcare use. Limitations of the reviewed studies include a lack of consistency in measuring anxiety and outcomes, a small number of longitudinal studies, and finally a lack of exploration of mechanisms underpinning the association.

The empirical paper explored how psychological mechanisms impact on asthmatics perception of breathlessness, quality of life, and control. Anxiety in asthma has been associated with perception of breathlessness, a cornerstone of asthma management. The experimental study used a Methacholine Test (MCT) to reduce lung function to 80% to induce bronchoconstriction to explore the effect of reduced lung function on anxiety, breathlessness, asthma quality of life, asthma control and association with attentional resources. Attentional bias was measured by a computer task (Attentional Network Test, ANT) and a self-report (Attention Control Scale, ACS). 31 participants were recruited for the study. Changes in breathlessness were noted across conditions, independent of lung function. Breathlessness was associated with anxiety and not with Asthma Quality of Life (AQLQ) or their asthma control. In a blockwise regression analysis, anxiety was a significant predictor of quality of life and control of asthma. Perceived breathlessness or anxiety was not significantly associated with attention as measured by ANT, though anxiety was associated with self-reported measures of attentional shift and focus. Subsequently, increased breathlessness during bronchoconstriction revealed a decrease in shifting attention. Attention could be a mechanism to target in improving asthma care; however, further research is needed. Limitations, clinical implications, and future directions for research are discussed.

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Declaration of Authorship

I, Hasina Khatun, declare that this thesis entitled “Using the methacholine challenge to determine how psychological mechanisms impact asthma symptom perception and quality of life” and the work presented in it are my own and have been generated by me as the result of my own original research.

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
5. I have acknowledged all main sources of help;
6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
7. None of this work has been published before submission

Signed:……

Date:……

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Abbreviations

ACM	Asthma Control Measure
ACQ	Asthma Coping Questionnaire
ACS	Asthma Control Scale
ACT	Asthma Control Test
AD	Asthma and Depression
AE	Accident and Emergency
ADIS-IV	Anxiety Disorders Interview Schedule for DSM-IV
ANSQ	Autonomic Nervous System Questionnaire
API	Acute Panic Inventory
AQLQ/ AQOL	Asthma Quality of Life Questionnaire
ASC	Asthma Symptom Checklist
ASiA	Adherence Schedule in Asthma
ASI-3	Anxiety Sensitivity Index-3;
ASQ	Asthma Symptom Questionnaire
BDI	Beck's Depression Inventory
BNSQ	Basic Nordic Sleep Questionnaire
BTS	British Thoracic Society
CAS	Catastrophizing about Asthma Scale
CBT	Cognitive Behavioural Theory
CISS	Coping Inventory for Stressful Situations
COPE	Coping Orientation to Problem Experienced
DSQ-40	Defence Style Questionnaire
ED	Emergency Department
FCZ	Formal Characteristic of Behaviour
GAD	Generalised Anxiety Disorder
GHQ-12	General Health Questionnaire 12
GHQ-28	General Health Questionnaire – 28
GINA	Global Initiative for Asthma
GP	General Practise
HADS	Health Anxiety and Depression Scale
HAMA	Hamilton Anxiety Rating Scale
HAMD	Hamilton Depression Rating Scale
HQOL	Health Quality of Life
ICD-10	International Classification of Disease 10
IECS	Internal – External Control Scale
LAQ	Living with Asthma
LSI	UCLA Life Stress Interview
LOC	Locus of Control
M.I.N.I	Mini International Neuropsychiatric Interview
Mini-AQLQ	Mini Asthma Quality of Life
MPS	Maudsley Personality Scale
NAD	Neither anxiety or depression
PAS	Panic and Agoraphobia Scale
PHQ	Patient Health Questionnaire
PANAS	Positive and Negative Affectivity Schedule
PD	Panic Disorder
PTSD	Post-Traumatic Stress disorder
PSS	Perceived Stress Scale
QOL	Quality of Life
RAPBC	Revised Asthma Problem Behaviour Checklist
SAS	Zang Self-rating Anxiety Scale

SDS	Zang Self-rating Depression Scale
SF-12/ SF-36	Short Form 12/36 Health Survey Questionnaire
SGRQ	St. Georges Respiratory Questionnaire
SIGN	Scottish Intercollegiate Guidelines Network
SPTZ	Spitzer Binary Assessment
STAI	State and Trait Anxiety Scale.
SSAS	Somatosensory Amplification Scale
VAS	Visual Analog Scale

Chapter 1: Systematic Literature Review: The relationship between anxiety and asthma, and the impact on outcomes.

1.1 Introduction

Asthma is a chronic medical condition, which clinically affects the airways, obstructing airflow within the lungs and causing the patient to suffer numerous symptoms. Key symptoms of asthma include breathlessness, chest tightness, coughing and wheezing (Rees, Kanabar, & Pattani, 2013). The fundamental pathology of asthma is inflammation (thickening) of the airways in the lungs causing it to narrow and cause asthma symptoms (bronchoconstriction). The Global Initiative for Asthma (GINA) postulates asthma can be triggered by environmental stressors, such as pollen, dust mites or physical exertion. This instigates irritation by responding to stimuli present in the system, resulting in increased mucus (GINA, 2017). There are two processes that contribute to bronchoconstriction: inflammation and mucus.

With a diagnosis of asthma exacerbation, the symptoms are particularly present during evening and early morning, feasibly triggered by exercise or allergen exposure and with a FEV1 ratio > 0.75 – 0.80 in adults. The Scottish Intercollegiate Guidelines Network (SIGN) defines FEV1 is a measure of a person's forced expiration to full capacity, in the first second. Methods of asthma assessment are variable: spirometry is a method for identifying airflow obstruction, or direct challenge using methacholine for confirmation (SIGN, 2016). Not all diagnoses of asthma are confirmed through lung function. Exacerbation is when symptoms have become acute, which can signify a lack of control or adherence to medication. Furthermore, this is common in high-risk people, and can be fatal if left untreated, with three people dying every day in the UK due to asthma (Asthma UK, 2016a; Rees et al., 2013).

1.1.1 Management of Asthma

The management of asthma is multifarious, with a significant burden of care placed not only on patients and families, but also on general practice, outpatients and inpatient care (SIGN, 2016). Pharmacological input is based on the severity of asthma, using a combination of preventative and/or reliever inhalers, dependent on one's asthma care plan. Guidelines for treatment and management are based on several sources and the country of treatment, such as the British Thoracic Society (BTS), SIGN and GINA. Briefly, management of asthma includes medication, prescribed inhalers, treating modifiable risk factors and employing non-pharmacological strategies. The National Institute for Health and Care Excellence (NICE) provides guidelines based on BTS/SIGN on the care plan for asthma. Medication can be used on a daily basis for preventative purposes, or consist of steroid based inhalers to reduce inflammation during an asthma attack (NICE, 2013). Asthma guidelines advise medical professionals to provide a personalised action plan to encourage self-management; failure to manage leads to asthma attacks and possible hospitalisation.

1.1.2 Prevalence of Asthma in the Population

Around 235 million people suffer from asthma globally, including 5.4 million people in the United Kingdom (UK), of which 4.3 million are adults (Asthma UK, 2016b; World Health Organisation, 2017). Asthma statistics suggest that the prevalence plateaued in the 1990s, however, current statistics indicate the UK to have the greatest prevalence of asthma sufferers in the world. The NHS currently spends £1 billion yearly treating and managing asthma. Given that exacerbations hospitalise someone every eight minutes in the UK, there is a strong need to reassess our understanding of poor asthma outcomes (Asthma UK, 2016a). There are several

factors that influence poor outcomes in asthma, such as age (Cooper et al., 2007), gender (Woods, Sorscher, King, & Hasselfeld, 2003), economic status (Nunes, Pereira, & Morais-Almeida, 2017), psychosocial (Wright, Rodriguez, & Cohen, 1998), and psychiatric/ psychological factors (Lavoie et al., 2016). Anxiety in particular has shown to be six times as common in people with asthma as matched controls (Thomas, Bruton, Moffatt, & Cleland, 2011), which will now be considered specifically.

1.1.3 Anxiety

Anxiety has been defined in many ways, though there is considerable overlap between definitions (Strongman, 1995). For instance Freud (1975) defined anxiety as an unpleasant state and used words such as 'nervousness, apprehension or anxious expectation', similarly Edelmann, (1992) also denotes anxiety as tension, uneasiness, un-pleasurable state, fear, and worry, an emotion that is evoked based on subjective interpretation of danger. Behavioural theorists postulate that anxiety is the mediating mechanism that denotes avoidance of threatening stimuli. This is in line with state anxiety, which is characterised by anxiety for a short period, fluctuating in the intensity of the emotion subject to several factors (Spielberger, Gorsuch, & Lushene, 1970). Beckian models of anxiety have theorised that anxiety is interpreted based on previous interactions with the world. This is then processed using cognitive mechanisms (e.g. memory and attention), and can be expressed behaviourally and/or physiologically. Individuals with anxiety witness external threat-related stimuli that evokes associated irrational beliefs, and these elicit emotional, physiological (e.g. raised heart rate, sweaty palms), and behavioural fight or flight response (Ellis, 1962; Wells, 1997). Furthermore, cognitive theorists describe anxiety as a personality trait that influences cognitive processing (Cattell & Scheier, 1961; Spielberger, 1972). For

instance, those with higher levels of trait anxiety have more organised worries in their long- term memory or low trait anxiety, and that this influences the structure and cognitive processing (e.g. efficient retrieval of memories). According to Eysenck's theory, varying degrees of anxiety explain the differences in the cognitive appraisal of ambiguity (Salkovskis & Warwick, 2001).

Empirical studies have highlighted the association between anxiety and physical health conditions, such as asthma. The prevalence of anxiety symptoms and/or disorders in the asthma population ranges from 10 % to 44% (Leng et al., 2015; Quon et al., 2015)

1.1.4 Prevalence of Psychiatric/Psychological Comorbidity in Asthmatics

The prevalence of psychiatric disorders / psychological symptoms in asthma has been well documented, along with the impact this has on the management of asthma (Kollowitz, Kanniess, Dahme, Magnussen, & Ritz, 2007). Chronic disorders, including asthma, are associated with the increased risk of mental health difficulties (Oga et al., 2007). Prevalence of psychiatric disorders is greater in the severe asthma population, with 49% of asthmatics fulfilling the psychiatric diagnostic criteria for International Classification of Disease 10 (ICD-10) (Heaney, Conway, Kelly, & Gamble, 2005). The prevalence of psychiatric disorders were particularly high on the following disorders; depressive disorder, Generalised Anxiety Disorder (GAD), phobia and Post-Traumatic Stress disorder (PTSD), and a lower prevalence of personality disorders. Furthermore, a recent cross-sectional study highlighted that 31% of the asthmatic sample had a psychiatric disorder (Lavoie et al., 2016).

Systematic reviews have highlighted the prevalence of depression, which is associated with increased non-compliance, increased perception of symptoms and triggers (Zielinski et al., 2000), specific symptoms linked to depression (Opolski &

Wilson, 2005) and decreased quality of life (Filipowski, Bozek, Kozlowska, Czyżewski, & Jarzab, 2013). Furthermore, depression and anxiety were reported to account for the lack of accuracy in judging triggers and therefore impacting on a range of outcomes. A complex process plausibly mediated by numerous variables in inaccurately identifying stimulus. Incorporating emotional difficulties, such as depression or anxiety, could enhance this complex relationship, heighten perception and/or contribute to bronchoconstriction (Janssens & Ritz, 2013).

The prevalence of anxiety or Panic Disorder (PD) has been consistently reported, with substantial developments in research exploring the prevalence of anxiety in the asthma population. A cross-sectional study reported that 41% of aspirin-induced asthmatics suffered from PD (Potoczek, 2011). A national study in the UK identified the prevalence of anxiety in asthmatics at 59% (15.7% for asthma-specific panic fear) (Cooper et al., 2007). This review is therefore interested specifically in the impact anxiety has on asthma related outcomes, such as quality of life.

1.1.5 Psychological Theories of Anxiety and Panic

Numerous models of anxiety and panic exist. For the purpose of this review two models will be considered because of their relevance to asthma and anxiety relationship (Thomas et al., 2011). Specifically, the cognitive models of panic (Clark, 1988) and health anxiety/hypochondriasis (Warwich and Salkovskis, 1990) will be discussed in relation to asthma and hypothetical examples given with supporting references from the literature where possible. Discussion on classical conditioning, early conceptualisation of anxiety, can be found in Appendix A.

The panic model proposed by Clark (1988) includes sequences of events that precede a panic attack. Some symptoms of panic include trembling, shaking, nausea,

respiratory difficulties. Clark proposed circular events to depict the precipitating and maintaining factors of panic. Clark's panic model proposes the 'trigger' is a feared stimulus or situation that has the ability to activate anxiety and/or a panic attack. The trigger is actively avoided, using safety behaviours; these are strategies employed by the individual to actively avoid confronting the feared stimuli. Negative beliefs are left unchallenged as a consequence (Salkovskis, 1991). Negative beliefs are embedded in schemas, which are cognitive structures or pockets of information that are developed through interaction with the world. Schemas help to organise and appraise new information and situations (Beck et al., 1985; Wells, 1997).

Triggers according to the panic model in relation to the asthma population can potentially be 'running' or a 'dusty room'; should they encounter these situations, a vicious cycle might ensue. Furthermore, the trigger can be internal, such as a 'tingly feeling in the chest' or being vigilant for bodily symptoms. Individuals with a history of panic are vigilant for bodily sensations. According to the model, when an individual is unable to control, avoid, or reduce bodily sensations, this activates their maladaptive schema and subsequent catastrophic misinterpretation of their bodily sensations can occur. The panic model argues that individuals will attend to sensations that others are not aware of due to their sensitivity to symptoms (Edelmann, 1992). The misinterpretation will raise the fear and continue to increase symptoms of panic (bodily symptoms); they will continue to practise strategies to control and avoid these bodily sensations, limiting the quality of their life and leading to negative emotions. Prevention of panic attack might be achieved by adopting appropriate cognitive and behavioural strategies, such as hyper vigilance and/or avoidance (Beck, Emery, & Greenberg, 1985).

In the context of asthma, the safety behaviour can be manifested as a reluctance to engage in physical activity such as running as the individual may hold a maladaptive schema that indicates 'running will cause an asthma attack'. For example, a person may be in a situation that requires for them to run for a bus, an activity they will usually avoid, this may cause slight breathlessness as they are not accustomed to exercising. In the asthmatic population, individuals with susceptibility to panic may have a tendency to be vigilant for bodily sensation and any changes can be interpreted as threats. In response to the bodily sensations they do not want to experience they may overmedicate (Lehrer, Feldman, Giardino, Song, & Schmaling, 2002; Rietveld & Creer, 2003). This may fail to work as the symptoms are not related to their asthma, but are symptoms of a panic attack that are not too dissimilar to those of an asthma attack (Thomas et al., 2011).

This will activate catastrophic thoughts such as 'I can't breathe; I'm going to die'. There is an appraisal of danger that activates the survival mechanism and to employ appropriate strategies. Further accelerating panic and in response they may continue to employ their safety behaviour of taking their asthma inhaler (over-medicating), taking in extra breaths, and/or accessing emergency services. In the instance strategies have not worked, a panic attack will ensue. Additionally, hyperventilating, symptom of panic attack can invoke bronchoconstriction continue to feed into the panic cycle (Blake & Kelly, 2006). In summary, Clark's model proposes that three factors maintain anxiety: selective attention to bodily events, safety behaviours and avoidance.

Drawing on Clark's (1988) panic model, a cognitive model of hypochondriasis and health anxiety was developed (Warwick & Salkovskis, 1989; Wells, 1997). The panic model is characterised by imminent threat; however, a distinguishing feature of

the health-anxiety model is that threat can also be in the distant future to provoke anxiety. For example, 'I am going to have bronchospasms', anxiety can be provoked due to the distant possibility of it occurring. With milder forms of health anxiety, worry dissipates with the reductions in symptoms, whilst beliefs about the presence of serious illness remain with severe forms. Warwick and Salkovskis's model incorporates four factors: cognitive, affective, behavioural and physiological (Figure 1).

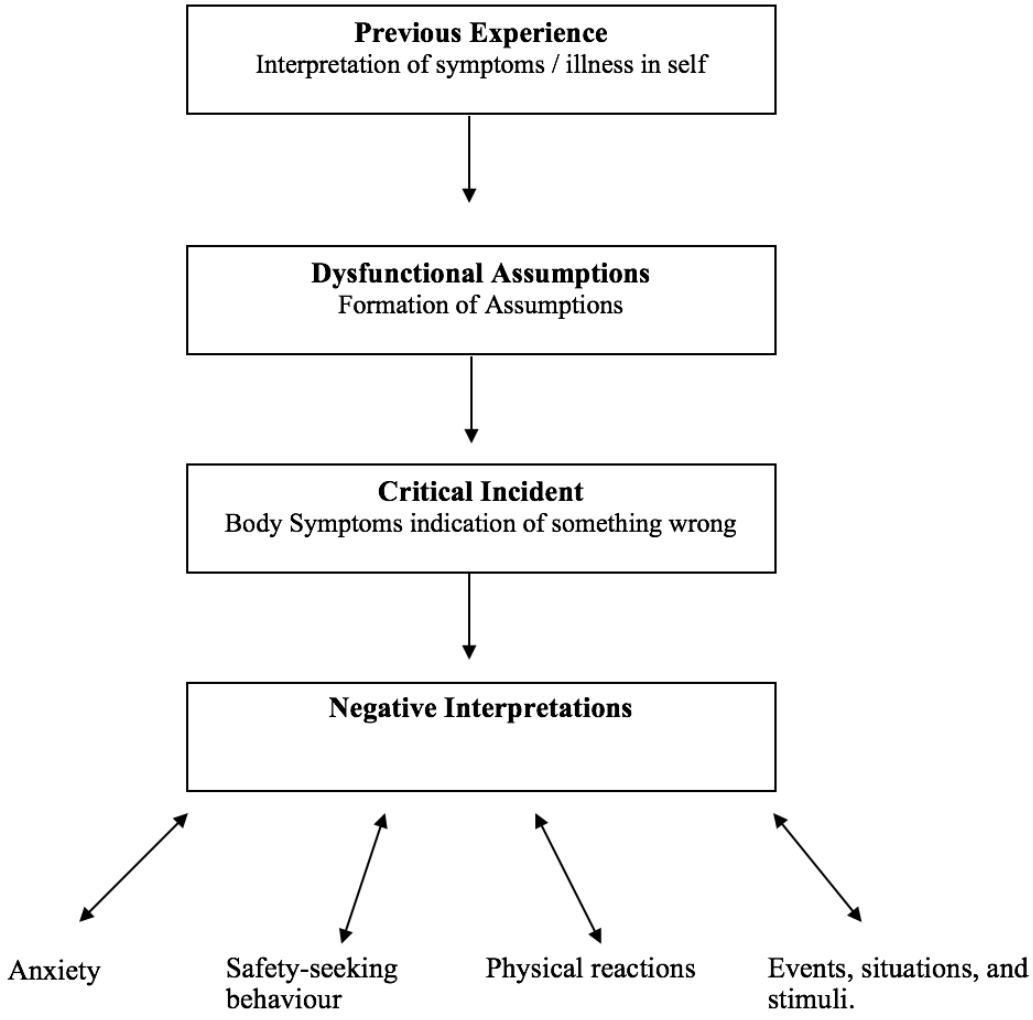


Figure 1. Health Anxiety Model adapted from Warwick and Salkovskis, (1990) and Salkovskis and Warwick (2001). The model incorporates a cognitive behavioural framework.

The health anxiety model proposes that health anxiety is caused by an enmeshment between assumptions about health related illness and a critical incident. New critical incidents activate the dysfunctional assumptions that inform negative interpretations that keep mood and safety seeking behaviour in place. Negative interpretations are developed based on a combination of four perceived factors: probability of illness, awfulness, ability to cope, and the extent to which external factors will help. In asthma, schemas are developed based on the individual's previous experience of asthma such as 'asthma related symptoms of bronchospasm, coughing, sensations in the chest, etc. are not good', or 'previous unsatisfactory medical treatment of chest infection so need to double check myself' (Warwick & Salkovskis, 1990). Dysfunctional assumptions may have developed as, 'coughing precludes a chest infection, and therefore coughing is a sign of something terrible'. New critical situation ensues and subsequent negative interpretation. This can potentially lead to constant body checking (e.g. monitoring breathing), hypervigilance, seeking consultation with medical professionals, and due to the anxious reactions, physiological symptoms could appear that validate their belief that something is wrong (Salkovskis and Warwick, 2001). Kellner (1985) postulates that an inaccurate perception of symptoms can rapidly develop into 'danger' for the individual.

Maintaining the negative misinterpretation involves engaging in several behaviours: checking, avoidance, safety behaviours, and reassurance seeking. Bodily checking possibly includes taking deep breaths to check that the lungs are functioning properly, thus increasing the probability of muscular and chest strain (physiological changes) that are similar to asthma symptoms. The safety seeking behaviours used by individuals can increase symptoms that were the foundation of their initial

misinterpretation (Salkovskis & Warwick, 2001). Further examples of engagement of safety behaviours or reassurance seeking can include, respectively, administering extra medication for the former behaviour or visiting primary health care facilities to prevent a potential exacerbation/asthma attack or to seek reassurance. Anxiety can remain irrespective of reassurance or safety behaviours in health anxiety. Additionally, where there is a potential to misinterpret the situation as imminent threat and this can lead to panic.

Research has also highlighted the importance of cognitive processes, such as attention in the role of appraising threat as part of the health anxiety model (Foa & McNally, 1986). Other models have also explored alternative underlying mechanisms such as 'memory biases', focusing on threat related memory (Coitre Shear, Cancienne, & Zeitlin, 1994), and 'interpretive biases', which refer to interpreting stimuli based on an individual's anxiety disorder type (Clark et al., 1997).

The areas of functioning, as discussed by the model, can be measured using validated outcome measures, such as the Asthma Quality of Life Questionnaire (AQLQ) and the Asthma Control Questionnaire (ACQ) in asthmatics.

1.1.6 Outcomes

Quality of Life (QOL) is a multifarious concept, comprising subjective appraisals of several domains on burden of disease on a patient's life. QOL is a difficult concept to define; it has historically provided a metric for quantifying the following domains: health status, functional status, and social and emotional functioning (Wilson et al., 2012). Labelling of the domains will vary between each QOL measure; however, essentially they will cover similar areas (Felce & Perry, 1995). Functional status encapsulates the ability to function in the daily routine (e.g. completing housework). Health status is the frequency and intensity of the physical

health symptoms, which in asthma account for the need for medical care. Social functioning focuses on society or professional activity, while emotional functioning focuses on the emotional impact of the disease.

Asthma control is a further outcome measure that conceptualises asthma control and change in control. Ideal asthma control involves curtailing symptoms, activity limitations, bronchoconstriction and use of rescue inhalers (Juniper, O'Byrne, Guyatt, Ferrie, & King, 1999). An additional outcome measure is the Asthma Symptom Questionnaire (ASQ), which quantifies the subjective perception of symptoms in an asthma attack.

There are other variables, such as lung function, healthcare utilisation and dyspnea that have been included in the review as a result of being included in papers that were selected for the review.

In summary, the role of anxiety in this population and the impact it has on outcomes, such as quality of life, healthcare use, asthma control and symptoms, has been widely published. Studies have identified correlations between anxiety symptoms/disorders and quality of life, asthma (Avallone, McLeish, Luberto, & Bernstein, 2012; Lomper, Chudiak, Uchmanowicz, Rosińczuk, & Jankowska-Polanska, 2016) and presentation of asthma related symptoms (Goldney, Ruffin, Fisher, & Wilson, 2003). Other studies have found no relationship between asthma control and anxiety symptoms (Trzcinska Zwierzchowska, Kozlowski, Derdowski, & Przybylski, 2013). However, attempts to synthesise the literature on anxiety and asthma have been fragmented, lacking in structure and are now dated, with the last review in this area published in 2004 (Katon, Richardson Lozano & McCauley, 2004)

1.1.7 Aims and Research Questions

The purpose of this narrative review is to provide an up-to-date synthesis of the evidence for anxiety disorders or symptoms in adults with asthma in a consensus manner arranged according to the impact the association has on outcome variable reported. Previous reviews on anxiety and asthma are dated (Katon et al, 2004; Ten Thoren & Petermann, 2000). The review will further provide a structured summary and critique of the evidence in relation to psychological theory. An understanding of the impact of anxiety in asthmatics has the potential to act as a foundation for the development of psychological therapy as a treatment, avenues to improve quality of life, control of asthma, or as a means of avoiding overuse of medication. Morbidity in asthma arises primarily due to poor management of the disease, particularly in relation to the use of preventative medicine (Katon et al., 2004). Finally, the review aims to further identify gaps in the literature, which may warrant further research.

1.1.7.1 Review Questions:

1. Is there an association between anxiety and asthma?
2. What is the impact on outcomes measures, such as quality of life and control, due to the association between asthma and co-morbid anxiety?
3. What are the gaps in the literature?

1.2 Methods

1.2.1 Search Strategy

Four electronic databases were utilised to identify studies for this review and capture a variety of publications from both psychological, medical, and nursing backgrounds. Two searches were completed through EBSCO, they were PsychINFO and CINAHL. Further two databases were PubMed and Web of Science (WOS). The databases cover literature from various fields: PsychInfo is a database from the field

of psychology, CINAHL encompasses literature from nursing, PubMed is a database of science literature that comprises of research from several allied medical professionals, and WOS provides literature from fields of social sciences, sciences, arts, humanities and other scientific disciplines. The search terms were partially generated using the previous literature review, partially from preliminary examination of key words during scoping of literature, and partially from the thesaurus. The search terms are summarised in Table 1 (Katon et al., 2004). No restrictions on publication date were applied initially.

Table 1
Terms used for Literature Search

	Anxiety	Asthma	Exclusion (not)	Limiters
Search Terms	Mental Health / Disorders	Asthma	Smoking	English
			Child*;	Peer Reviewed
	Psychiatric Disorders		Pediatric;	Journals only
	Psychological Consequence		Paediatric; Youth; Young	Quantitative
	Anxiety; Generali*ed Anxiety Disorder; Anxiety Disorder; Social Anxiety; Panic Disorder; Panic; Panic Attack		People; Teen*; Adolescent	Adults only
				Pregnant
			Animal	
			Pregnant Woman	
	Depress*/ Major Depression		Other chronic conditions	
	Psychological Dysregulation; Cognitive Bias			

The search was organised by two concept blocks, the first concept block listed mental disorders. Terms were *Mental Health / Disorders* or *Psychiatric Disorders / Consequence* or *Anxiety" or Generali*ed Anxiety Disorder* or *Anxiety Disorder* or

Social Anxiety or *Depress**, *Panic Disorder* or *Panic* or *Panic Attack* or *Psychological Dysregulation* or *Cognitive Bias.* The aim was to identify all papers that potentially have utilised an anxiety measure.

The second concept block included one search term relating to asthma, *Asthma*, to capture the target population. The two concept blocks were combined with 'and'. This was to limit records to measuring a psychological variable of anxiety with asthma. In instances where databases varied in the use of asterisk for terms, the variations were spelled out (Sampson et al, 2009). This produced 11,176 records prior to applying restrictions; the selection process has been documented systematically (see Figure 2).

To remove extraneous variables that may influence the management of asthma, *Smoking* was entered as a 'not'. Search terms of *Child*, Pediatric Paediatric, Youth, Young people* or *Adolescent* or *Teen** were used to further exclude records pertaining to children sample and only permitting adult sample studies to be yielded. Additional restrictions to exclude records not published in English and qualitative research. The restrictions on the search criteria reduced the records to 2,542. Records were restricted to peer reviewed journals. There are benefits and limitations in the inclusion of grey literature in a review, grey literature enables bridging gaps in literature and reduce publication bias (Pappas & Williams, 2011). However, grey literature was not sought for this review as there is a risk of overestimating the findings and given the literature is not peer reviewed there is a risk of lower quality assurance (Saleh, Ratajeski & Bertolet, 2014)

1.2.2 Search Criterion

1.2.2.1 Inclusion Criteria. Each study was required to meet the following criteria in order to be eligible for inclusion in the literature review:

1. Explored impact of asthma and anxiety, on outcomes using validated measures. Outcome measures include quality of life, symptom perception, subjective and objective control of asthma, and lung function assessment.
2. Included a sample of working age adults (>18 to <70) with a formal diagnosis of asthma and have anxiety symptoms or disorders
3. Papers published from January 2004 and onwards
4. Available in English language until 30th December 2016

1.2.2.2 Rationale for Inclusion Criteria. Types of measures: Studies were included based on the criteria that asthma was explored in relation to a validated measure of anxiety in relation to outcome research. It therefore excluded studies that were not looking beyond the prevalence of anxiety in asthma, where no statistical analysis took place between asthma, anxiety and an outcome measure.

Participants*:* Further inclusion criteria were adults aged between 18-70 years. This excluded adolescents as this review was focused on adult population of asthma sufferer and adults over the age of 70. The rationale attributed to excluding participants over 70 years of is in the context of declining cognitive abilities and the presentation of mental illness can differ significantly in older age (Fiske Wetherell, & Gatz, 2010). Pregnant women and other chronic physical conditions were also excluded as extraneous variable. Both of these groups will bring associated co-morbidity that will interfere with outcomes.

1.2.2.3 Diagnosis. By including other search terms that were not 'anxiety', such as depress* and psychological dysregulation, the database included studies pertaining to exploring anxiety but not denoted as a key world. This allowed for greater prospect of anxiety papers being included. However, also a relatively substantial number of papers were not anxiety related as a result. Further exclusion

criteria were introduced to exclude Posttraumatic Stress Disorder (PTSD) and other psychiatric disorders. In principle any disorders that were not categorised under anxiety in the DSM-IV^{TM} (APA, 2013) were excluded from research criteria.

An additional criterion required participant population to hold a formal assessment or diagnosis of asthma, therefore excluding papers where only self-report asthma was reported.

1.2.2.4 Study Design. The review excluded papers that were not empirical studies in peer-reviewed journals. Furthermore, the emphasis was on the exploration of a relationship between asthma, anxiety and outcome measures, only allowing for quantitative papers. This meant the exclusion of reviews, posters, qualitative and case studies. This further excluded invention, medication and validation studies. All duplicates and animal studies were also removed from the study.

1.2.2.5 Year of Publications. At the point of full text review, the relative numbers of studies were beyond the scope of this literature review and therefore they were restricted to include only publications from 2004. 2004 was deemed to be the appropriate year as this was when the most recent review in this area had been conducted and therefore any research prior to 2004 most likely have been reviewed previously (Katon et al., 2004)

1.2.3 PRISMA Flow Diagram

The process of identifying and screening records for reviews was conducted by one independent reviewer. Figure 2, illustrates the flow of records retrieved from the four databases and process of inclusion and exclusion using a PRISMA flow diagram (Moher, Liberati, Tetzlaff , Altman & Prisma Group, 2009). Initial search prior to restriction being applied produced 11,176 record; PsychInfo (968), CINAHL (238), PubMed (6,057) and Web of Science (3,913). Subsequent removal of records

with the use of limiters resulted in 2,542 papers, in additional record was identified through other sources beyond the electronic searches. Consequent removal of duplicated records, resulted in 2051 records for title and abstract screening.

Records were eliminated primarily at this stage dependant on participant sample, no anxiety and other criterion dependant on title and abstract. The remaining 294 records were subsequently given a full review and using the criteria judged as to their acceptability. The remaining 26 papers from the search process are included in this review.

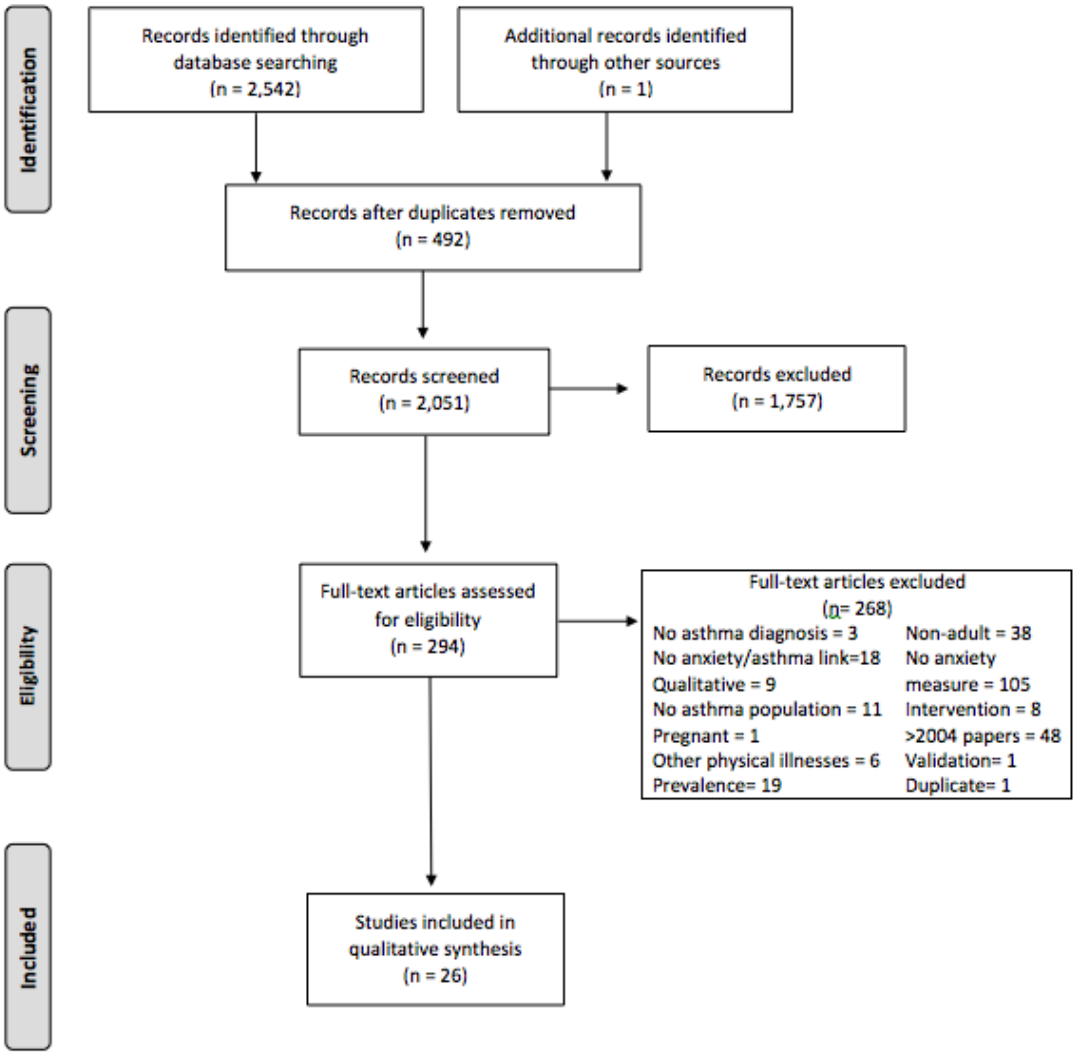


Figure 2. Selection Process of Articles for Narrative Review in a PRISMA Flow Diagram

1.3 Results

1.3.1 Design

The criteria allowed for only quantitative papers to be included. The results consist of 20 cross-sectional studies, four experimental studies and two longitudinal studies. These 26 articles restricted the population to physician-confirmed diagnoses of asthma in the adult population. The articles also contain validated measures of anxiety concomitant with a second outcome variable. Numerous studies contained more than one outcome variable and consequently contributed to more than one category. Themes that emerged developed the following five categories: asthma quality of life (*n* = 11), perception of control (*n* = 16), healthcare utilisation (*n* = 8), lung function (*n* = 7), and dyspnea (*n* = 6).

1.3.2 Study Characteristics

Table 2 outlines the salient characteristics of the studies selected for the literature review. Appendix B holds a table on quality appraisal of each paper, quality assessment was based on the criteria from a previous peer reviewed systematic review on chronic health (Schoth & Liossi, 2016).

The majority of the measures of anxiety pertain to anxiety symptomology (*n* = 22), while the remainder of the studies identified diagnoses of PD (Boudreau et al., 2015; Feldman, Siddique, Thompson, & Lehrer, 2009; Schneider et al., 2008) and Anxiety (Pilipenko, Karekla, Georgiou, Feldman, 2016; Wang et al., 2010). There were differences in the way anxiety was quantified; tools ranged from self-report, Health Anxiety and Depression Scale (HADS) to a structured interview diagnostic tool (Anxiety Disorders Interview Schedule for DSM-IV [ADIS-IV]).

Studies were conducted internationally; only one study took place in the UK. Poland was the most common country in studies included for this review.

Of the 26 papers, eight publications overlapped in terms of the authorship and/or clinical setting. Two authors appear in two publications as both first and corresponding authors, Giorgio Ciprandi (Ciprandi et al., 2015; Ciprandi et al., 2016) and Steven De Pueter (De Pueter et al., 2007;De Pueter et al., 2008). The remaining 6 publications had overlapping authorship on publications; Mariusz Furgal and Roman Nowobilski (Furgal et al., 2011; Nowobilski et al., 2015), Antje Kullowatz and Thomas Ritz (Kullowatz et al., 2007; Ritz et al., 2014); and finally Gang Wang and Yu-Lin Ji (Yang et al, 2016;Zhu et al, 2016). The overall results may therefore not be as generalizable as they first appear, as recruitment of the samples could potentially come from the same clinic. However, this was difficult to determine as the publications did not provide sufficient information on place of recruitment other than outpatients department for asthma.

Table 2
Characteristics of Studies

Study	Country	Design and aim	Sample Size *n* & Gender	Mean Age & SD	Anxiety Measure	Outcome Measure	Findings
Avallone et al., 2012 Affiliations: Department of Psychology, University of Cincinnati	USA	This cross-sectional study hypothesised that anxiety sensitivity would predict asthma control and quality of life.	*N* = 127 F: 74% M: 26%	*M* = 43.34 *SD* = 12.29	ASI-3	PANAS ACT Mini-AQLQ	Anxiety sensitivity, physical concern, was associated with asthma control and quality of life negatively. Asthma sufferers who are more likely to report a fear of physical sensation will likely report poorer asthma control and lower levels of quality of life.
Boudreau et al, 2015 Affiliations: Montreal Behavioral Medicine Centre, University of Qubec, Concordia University, & Canadian Institute of Health Research, FRSQ	Canada	This experimental study explored the impact of MCT on asthmatics with PD and hypothesised to exhibit greater subjective distress and airway responsiveness compared to non-PD asthmatics.	F: 70% M: 30%	*M* = 44 *SD* = 14 *M* = 51 *SD* = 14	ADIS-IV ASI	ACQ PSS BORG VAS	There is a significantly higher number of emergency visits and duration of asthma in the PD group. Greater drop in FEV_1 following MCT in PD group. PD group also reported greater anxiety symptoms following MCT. No difference in control scores.
Ciprandi et al., 2015 Affiliations: IRCCS - Azienda Ospedaliera	Italy	This cross-sectional study explored the effect of anxiety and	*N* =263 F: 59% M: 41%	*M* = 39.2 *SD* = 16.1	HADS	ACT	Patients with higher anxiety level have significantly lower perception of control (act) than those with lower anxiety. Weak negative

Universitaria San Martino, University of Genova, & University of Torino		depression on asthma in real life settings.				Control level (GINA)	correlation between ACT and anxiety. Uncontrolled asthmatics had highest level of anxiety and depression.
Ciprandi et al., 2016 Affiliations: IRCCS - Azienda Ospedaliera Universitaria San Martino & University of Torino	Italy	This cross-sectional study explored the relationship between symptom perception and degree of bronchial obstruction (FEV_1).	*N* =388 F: 59% M: 41%	*M* = 39.7 *SD* = 16.2	HADS	ACT VAS	Perception of asthma symptoms, as reported by VAS, was positively correlated, to varying degrees, with bronchial obstruction. Perception of impaired breathing had above normal anxiety score- anxiety may negative affect asthma. Lower VAS (symptom perception), uncontrolled asthma, lower asthma control test and higher anxiety and depression.
De Peuter et al, 2007 Affiliations: Research Group for Stress - University of Leuven, Department of Pneumology - University Hospital Gasthuisberg	Belgium	One of the aims of this experimental study were to investigate the effects of anxiety and catastrophic thinking about asthma on dyspnea.	*N* = 25 F: 48% M: 52%	*M* = 38.5 *SD* = 13.6	PANAS Anxiety subscale (ASC)	ASC CAS	Higher trait anxiety was correlated with increased symptoms with decreasing lung functions – higher baseline anxiety (state) were significantly more sensitive than lower baseline. State anxiety was not sensitive to sensory symptoms.
De Peuter et al., 2008 Affiliations: Research Group Health Psychology & Department of Lung	Belgium	This experimental study used three experimental conditions to explored the link between	*N* =72 F:52.8% M:47.2%	*M* = 30.4 *SD* = 13.2	ASC scale PANAS	ASC CAS	Asthmatics who are prone to catastrophising during exacerbation report are more likely to report symptoms when they are salient. Histamine provocation further

Diseases - University Hospital		catastrophic thinking and symptom perception					suggests catastrophic thinking during exacerbation is related to perceptual sensitivity for symptoms of bronchoconstriction. During the control situation there was catastrophic thinking, suggesting CT can lead to over perception in ambiguous situations.
Deshmukh et al., 2008 Affiliations: Asthma Foundation – Australia, Woolcock Institute of Medical Research, The University of Sydney, & 3SydneyWest Area Mental Health Service- Australia	Australia	Cross-sectional study hypothesised anxiety and depression would be associated with AQOL, perception, and panic-fear.	*N* =110 F: 65.5% M: 34.5%	*M* = 42 *SD* = 16	HADS	AQOL ASC	Significant linear association between anxiety and all domains of AQOL & ASC. However, not with GP visit. The relationships were not observed with depression. Differences in the impact on AQOL and ASC domains with low or high anxiety. Higher anxious groups had significantly more GP visits and ASC domains. In addition, reported lower AQOL domains. The results were independent of age, gender, or smoking. No association reported with ED visits.
Di Marco et al, 2010 Affiliations: Universita` degli Studi di Milano, IRCCS Fondazione	Italy	This cross-sectional study hypothesised that anxiety and depression in asthmatics will	*N = 294* F: 67% M:33% Controlled	*M* = 49	HADS	ACT	Significantly higher levels of anxiety and depression in poorly controlled asthma. Gender differences, women more anxious and reported poorer control. FEV_1

Maugeri, Universita` degli Studi di Messina, & Seconda Universita` di Napoli, Italy		influence level of control, as measured by the ACT	*n* = 208 Poor Control *n* = 86	*SD* = 16 *M* = 56 *SD* = 17			was not associated with anxiety. Anxiety is one of the risk factors.
Feldman et al., 2009 Affiliations: Yeshiva University, Robert Wood Johnson Medical School, Wood Johnson University Hospital at Hamilton, & University of Medicine and Dentistry of New Jersey	USA	Explored the mediation models panic and asthma outcomes.	*N* = 48 F: 66.7% M: 33.3% Asthma & PD *n*= 21 Asthma only *n*= 27	*M* = 39.2 *SD* = 13.8	PHQ ANSQ ADIS-IV	AQLQ ASC	Illness specific panic was significant in PD asthmatic when compared to non PD asthmatic group. Illness specific panic-fear mediates the relationship between PD in asthmatics and poorer AQLQ. Patients with 2 or more primary care visits were associated with increased illness specific panic-fear. Asthma only group had a higher level of low generalised fear-panic than the PD group, this was reversed with high levels of fear panic.
Furgal et al., 2011 Affiliations: Jagiellonian University Medical College, University School of Physical Education, & Jagiellonian University	Poland	This cross-sectional study explored the link between asthma, dyspnea and locus of control in relation to wider context.	*N* =111 F: 74% M: 37%	*M* = 49.79 *SD* = 14.19	GHQ-28 (anxiety subscale)	LOC	Dsypnea and depression scale were positively correlated, not with anxiety. Anxiety scale has been found to positively correlate with dypnea and strong internal LOC amongst men. Interestingly, this was mirrored with external LOC in women. This means that internal LOC protects women from

							anxiety/psychopathology unlike men.
Kolawole et al, 2011 Affiliations: Obafemi Awolowo University & Lagos State University Hospital	Nigeria	The cross-sectional study explored the role of health quality of life in asthmatics.	*N* =81 F:39% M:42%	*M* =35.22 *SD* =14.36	HADS	Mini-AQLQ	Significant negative correlation between anxiety and quality of life total, particularly symptom, emotion and activity. Anxiety resulted in lower quality of life.
Kullowatz et al., 2007 Affiliations: Southern Methodist University, Hospital Grosshansdorf, & University of Hamburg	Germany	A cross-sectional study exploring the association between anxiety/ depression, quality of life and health care use. Furthermore whether depression contributed over an above anxiety.	*N* = 88 F: 52.3% M: 47.8%	*M* = 52.7 *SD* = 12.3	HADS	LAQ SF-12	The study focused on more on the roles of depression and the other variables. Anxiety only significantly accounted for general mental wellbeing (SF-12) and LAQ psychological wellbeing.
Lavietes, 2015 Affiliations: New Jersey Medical School	USA	Cross-sectional study hypothesised that the genesis of dyspnea experienced in acutely ill and stable may differ.	*N* = 32 F: 44% M: 56%	*M* = 38 *SD* = 7	API SPTZ	Borg (dyspnea) SASS	Perception of dyspnea correlated with panic and lung function tests. The API (anxiety) continued to be a strong predictor of dyspnea, even following stabilisation. The mechanisms producing dyspnea in acute and stable asthma differ.

Nowobilski et al, 2009 Affiliations: Jagiellonian University School of Medicine, Academy of Physical Education, Etablissement Public de Sante Mentale De la Vallee de l'Arve, & Jagiellonian University	Poland	A cross-section study exploring the relationship between dyspnea, personality trait and psychopathology in asthmatic population. In addition, the influence of gender.	*N* = 112 F: 66% M:34%	*M* = 49.7 *SD* =14.2	STAI	Borg (dyspnea) BDI HAMD MPI IECS	Women were reported to hold higher level of anxiety-trait / depression than men. No gender differences amongst asthmatic regarding dyspnea and FEV_1. Dyspnea and FEV_1 was significantly correlated. Anxiety state and trait (depression and neurotism) was reported to significantly correlate with dyspnea. Regression analysis, reported anxiety-trait to be a predictor for dyspnea. The association between duration of disease and dyspnea is moderated by anxiety-trait in men, however, not women.
Oga et al., 2007 Affiliations: Kyoto University, Kyoto-Katsura Hospital, Hikone Municipal Hospital, & Shiga University of Medical Science	Japan	Longitudinal study comparing the psychological status of patients with asthma and other outcome measures.	*N* = 87	*M* = 50 *SD* = 2	HADS	AQLQ SGRQ	Anxiety correlated significantly with change in AQLQ, SGRQ and depression.
Panek et al, 2015 Affiliations: Medical	Poland	In addition to exploring causes of asthma, the study explored the factors	Asthma *n* = 159 F: 62.3% M: 37.7	*M* = 50.40 *SD* =15.70 *M* = 44.45	STAI-X1 STAI-X2	BORG ($_{\text{perceived exertion}}$) ACT	Correlations between coping and anxiety (trait and state) measures showed positive correlations, particularly with avoidance and

University of Lodz		inducing and maintaining asthma exacerbation.	Control *n* = 122 F: 62.26% M: 37.74%	*SD* =16.28		CISS FCZ	distraction. Furthermore, temperamental components, such as activity and emotional reactivity. Asthma exacerbation correlated with control, increasing dyspnea and state/trait anxiety significantly. However, the levels of anxiety (and depression) weren't so high. No relationship between anxiety and duration of asthma. Increased activity with higher trait anxiety was connected to administration of drugs.
Pilipenko et al., 2016 Affiliations: The Institute for Family Health, New York, University of Cyprus, Nicosia General Hospital, & Yeshiva University, New York	USA/ Cyprus	This cross-sectional study explored the group impact of psychiatric comorbidity has on illness management, this being asthma control and emergency hospital utilisation elated to asthma.	*N* = 212 F: 65.1% M: 34.9%	*M* = 60.42 *SD* = 3.24	PHQ	ACM Number of hospital visits (0-1)	Mental health was associated with poorer asthma control. Anxiety explained a significant proportion of variance in asthma control. Anxiety is a risk factor for hospitalisation and ER visits, however, did not predict hospitalisation (although higher than controls). Anxiety did not predict asthma control, when age and gender were controlled.
Ritz et al., 2014 Affiliations: Southern Methodist	USA	This experimental study explored the potential relevance of acute psychosocial	*N* = 80 Asthma *n* = 39	*M* = 24.6 *SD* = 10.1	HADS	PANAS PSS	There was a degree of association between FeNO and anxiety. Low anxiety did not report any change in FeNO, however, with high

University, Universidad San Francisco deQuit eQuit co deUT Southwestern Medical Center at Dallas, & University of Michigan Medical Centre		stress on the airways of asthmatics.	Control *n* = 41	*M* =25.4 *SD* =11.6			anxiety there was a significant increase in FeNO from pre to post stress.
Schneider et al, 2008 Affiliations: University of Heidelberg & University of Hamburg	Germany	A longitudinal study exploring the impact anxiety and depression have on health care utilization and quality of life in the community.	*N* =256 F: 61.7 M: 38.3	*M* =56.3 *SD* =16.4	PHQ (panic & depressio n)	AQLQ	High prevalence of panic disorder in asthmatics, also a predictor of unscheduled emergency visits. No association between panic disorder and asthma severity.
Smith et al., 2009 Affiliations: University of Oxford, University of Queensland, Princess Alexandra Hospital, Mater Adult Public Hospital, & St Mary's Hospital	UK/ Australia	This retrospective cross-sectional study explored the health behaviours of ambulance users differed 'walk-in' users of Emergency Department (ED)	Ambulance *n* = 34 F: 65.71% M: 34.29% Walk-in *n*=95 F: 52.58% M: 47.42%	*M* = 40.4 *SD* = 16.3 *M* = 31.8 *SD* = 12.3	HADS	ACT	No significant difference between users in terms of anxiety, however, there was a difference with depression. Ambulance users reported a higher level of anxiety. Higher rates of ED and urgent care visits with anxious patients.
Smith et al, 2005 Affiliations: University of East Anglia, Norfolk and Norwich University Hospital NHS Trust, & Acle Medical Centre	UK	A cross-section study using severe asthmatics to explore the mediating characteristics between clinical recognised poor	*N*= 133 F: 73% M: 27% Compliant *n*= 41	Not Provided	HADS	LAQ RAPBC ACQ SF-36 GHQ-12	Anxiety was reported to be the only comorbidity factor independently associated with poorly controlled group.

		controlled participants and adverse outcomes.	Poorly Compliant *n*= 92				
Trzcinska, et al., 2013 Affiliations: Nicolaus Copernicus University in Torun	Poland	Cross-sectional study explored the degree of asthma control and psychological disorders in bronchial asthmatic.	*N*= 223 Controlled *n*= 93 Uncontrolled *n*= 130	Not Provided	STAI	AQLQ ACT BDI	No correlation between asthma control and state or trait anxiety. However, there was a significant correlation between control and depression
Vieira, et al., 2011 Affiliations: Federal University of São Paulo/Paulista School of Medicine,	Brazil	Cross-Sectional study explored the association between asthma control and psychological disorder in moderate and severe asthmatics.	*N*= 78 F: 66% M: 34% Controlled *n*= 29 Uncontrolled *n*= 49	*M* =47.4 *SD* =13.1	HADS	ACT AQLQ	Anxiety and HADS combined score were significantly associated with uncontrolled asthma.
Wang et al, 2010 Affiliations: Respiratory and Critical Care Medicine - Sichuan University, & Pneumology Group - Sichuan University, University of Pittsburgh Medical Centre,	China	This cross-sectional study explored the relationship between psychological status and Airway Hyper-responsiveness (AHR) in uncontrolled asthmatics.	*N*=168 F: 62.5% M:37.5% NAD *n*= 50 Anxiety	 *M* = 33.7 *SD* = 11.4 *M* = 41.3	SAS	ACT AQLQ SDS	Anxiety did not impact quality of life, however, an interaction of depression and anxiety was reported to impact AQLQ. No significant differences in AHR between the groups. Anxiety is associated with worse asthma control.

Clinical Research of Chinese Medical Association, & Doctoral Fund of Ministry of Education of China			*n*= 8 Depression *n*= 36 AD *n*= 74	*SD* = 6.8 *M* = 34.1 *SD* = 12.6 *M* = 42.2 *SD* = 12.5			
Yang et al., (2016) Affiliations: Zhongda Hospital Affiliated to Southeast University, & Huzhou 3rd Hospital	China	This cross-sectionl study explored the underlying mechanisms of psychological disturbances in asthmatics using genetics.	*N*= 318 Asthma *n*= 143 F:70.9%, M:29.1% Control *n*= 175 F:55.9%, M:44.1%	*M* = 39.11 *SD* = 14.98 *M* = 50.22 *SD* = 12.95	HAMA	HAMD ACT	Negative correlation of the ACT score with both anxiety and depression in asthmatic patients. The interaction between 5-HTT (LL) and BDNF (A+) appeared to increase the risk of anxiety.
Zhu et al, 2016 Affiliations: Respiratory and Critical Care Medicine - Sichuan University, & Pneumology Group - Sichuan University,	China	This study explored the underlying biological mechanisms of asthma and psychiatric difficulties.	*N*=80 Asthma *n*= 50 F: 64% M: 36% Control *n*= 30 F:73%		HADS	ACT AQLQ Blood/ cells	Patients with psychological symptoms reported significantly worse control level and quality of life than asthmatic with no psychological problems. Although anxiety and depression do not share identical neuroendocrine pathways, their biologic and clinical effects on immune system are similar. The effects of anxiety were not distinct

		M:8%	from depression.

Abbreviations: ACM = Asthma Control Measure; ACQ = Asthma Coping Questionnaire; ACT= Asthma Control Test; AD = Asthma and Depression; ADIS-IV= Anxiety Disorders Interview Schedule; ANSQ= Autonomic Nervous System Questionnaire; API= Acute Panic Inventory; AQLQ/AQOL= Asthma Quality of Life; ASC= Asthma Symptom Checklist; ASiA= Adherence Schedule in Asthma; ASI-3= Anxiety Sensitivity Index-3; BDI= Beck's Depression Inventory; BNSQ= Basic Nordic Sleep Questionnaire; CAS= Catastrophizing about Asthma Scale; CISS= Coping Inventory for Stressful Situations; COPE= Coping Orientation to Problem Experienced; DSQ-40= Defence Style Questionnaire; FCZ = Formal Characteristic of Behaviour; GHQ-12= General Health Questionnaire 12; GHQ-28= General Health Questionnaire – 28; HADS= Hospital Anxiety and Depression; HAMA= Hamilton Anxiety Rating Scale; HAMD; Hamilton Depression Rating Scale; IECS= Internal – External Control Scale; LAQ= Living with Asthma; LSI = UCLA Life Stress Interview; LOC= Locus of Control; M.I.N.I= Mini International Neuropsychiatric Interview; Mini-AQLQ= Mini Asthma Quality of Life; MPS= Maudsley Personality Scale; NAD= Neither anxiety or depression; PAS= Panic and Agoraphobia Scale; PHQ= Patient Health Questionnaire; PANAS= Positive and Negative Affectivity Schedule; PD= Panic Disorder; PSS= Perceived Stress Scale; RAPBC= Revised Asthma Problem Behaviour Checklist; SAS= Zang Self-rating Anxiety Scale; SDS= Zang self-rating Depression Scale; SF-12/ SF-36= Short Form 12/36 Health Survey Questionnaire ;SGRQ= St. Georges Respiratory Questionnaire; SPTZ= Spitzer Binary Assessment; SSAS= Somatosensory Amplification Scale; VAS= Visual Analogue Scale.

1.3.3 Prevalence of Anxiety

Of the 26 studies, 16 studies either reported (or provided sufficient information to calculate) the prevalence of asthma in the sample population of each study. The prevalence of anxiety symptoms or diagnoses ranged between 3.3% and 48%.

1.3.4 The Relationship Between Quality of Life Dimensions and Anxiety

In total, 11 of the studies contained quality of life and symptom related measures. Two of those did not perform statistical analysis between anxiety and quality of life in asthmatics (Ciprandi, Schiavetti, Sorbello, & Ricciadolo, 2016; Trzcinska et al., 2013).

Of the remaining nine studies, eight contained Asthma Related Quality of Life questionnaires (AQLQ) and one contained Health Quality of Life (HQOL) measure utilising different versions dependent upon the language of the study country. Two studies overlapped in authorship, with a total of three authors overlapping in both papers. Although the studies revealed opposing findings and had differences in methodology (Wang et al., 2010; Zhu et al., 2016). The studies recruited from across the globe (Germany, Australia, USA, and China) and the sample size varied from 48 to 256 (combined n = 1,045). The remaining study explored symptoms in relation to anxiety in asthmatics (De Pueter et al., 2007).

1.3.4.1 Significant Associations. Seven of the nine studies contained the AQLQ measure specifically, and six of those studies reported significant associations between total AQLQ and/or dimensions of the AQLQ and anxiety. The 7th study in this section explored mediation analysis.

Four studies reported associations of asthma related quality of life and anxiety symptoms (r^2 = 0.13: Deshmukh, Toelle, Usherwood, O'Grady, &

Jenkins, 2008; *r*= -0.60: Oga et al., 2007) or anxiety sensitivity (range: *r* = -.43 to .52: Avallone et al., 2012). Table 3 has a summary of effect sizes from associations. Deshmukh and colleagues (2008) reported significant linear associations between anxiety and lower scores on all dimensions of the AQLQ. Furthermore, the negative association of higher anxiety symptoms and lower quality of life scores reported a small effect size. Avallone et al. (2012) and Oga et al. (2007) reported large effect sizes on the associations.

Table 3
Effect Sizes of Associations between Anxiety or Panic and Asthma Related Quality of Life

Study	Quality of Life Measure / Domains	Effect Size
Avallone et al. (2012)	[2]AQLQ:	
	Activity Limitation	r = -.43*
	Symptoms	r = -.52*
	Emotional Functioning	r = -.46*
	Environmental Stimuli	r = -.49*
Deshmukh et al. (2008)	[1]AQLQ:	r^2 = .13*
	Activity Limitation	r^2 = .08*
	Symptoms	r^2 = .14*
	Emotional Functioning	r^2 = .15*
	Environmental Stimuli	r^2 = .13*
	Low/high anxiety and AQLQ	n^2 = .101
Feldman et al. (2009)	[3]AQLQ:	r = -.37*
	Activity Limitation	r = -.45*
	Symptoms	r = -.26
	Emotional Functioning	r = -.31*
	Environmental Stimuli	
Kullowatz et al. (2007)	[1]SF-12:	
	Physical Wellbeing	r^2 = .50
	Mental Wellbeing	r^2 = .47*
	LAQ:	
	Physical	r^2 = .65
	Psychological	r^2 = .60*
	Functional	r^2 = .61*

Kolawole et al. (2011)	[2]HQOL	r = -.31*
	Activity Limitation	r = -.28*
	Symptoms	r = -.07
	Emotional Functioning	r = -.28*
	Environmental Stimuli	r = -.28*
Oga et al, 2007	AQLQ:	r = -0.60
Zhu et al., 2016	AQLQ	Insufficient information

[1] Hierarchical Multiple Linear Regression Analysis, [2] Correlational Analysis, [3] Mediation Model, [*]Statistically Significant

Kullowatz et al. (2007) included two measures of quality of life in their study, with mixed results. There was a significant association with large effect sizes between anxiety and specific dimensions of quality of life such as function limitations, distress and psychological across both measures of quality of life. No significant associations were noted between anxiety and physical wellbeing on both measures of quality of life. Similarly, Kolawole and colleagues (2011) reported significant negative associations, excluding symptoms. As anxiety increased, significantly associated dimensions of quality of life were shown to decrease. Furthermore, Zhu and colleagues (2016) explored the AQLQ in asthmatics with psychological symptoms (including anxiety) and with controls, reporting a significant difference. However, anxiety was not reported independently and therefore such an association will prove difficult to comment on.

The final study in this category explored a mediation model for PD and AQLQ outcomes; the study reported reduced scores on all dimensions excluding symptoms (Feldman et al., 2010). The study concluded that illness specific panic fear mediated the relationship between total AQLQ scores and emotional functioning due to asthma.

1.3.4.2 Methodological Considerations. Two of the six papers reported the duration of asthma diagnosis (Kolawole et al., 2011; Kullowatz et al., 2007;). Only one study reported on type of asthma diagnosis represented by the participant sample (Kullowitz et al., 2007). Four of the studies used the same quality of life instrument, while the remaining two utilised different quality of life measures, making classification and generalisation inconsistent (Kullowatz et al., 2007; Kolawole et al., 2011). All the studies explored trait anxiety and not state, enabling easier comparisons. Limitations with sample selection may also impact on findings, due to using a homogenous sample (Avallone et al., 2012) or lack of power calculations (Avallone et al., 2012; Feldman et al, 2010; Kullowatz et al, 2007). However, the inclusion of a longitudinal study improves the quality of studies, supporting the link between anxiety and quality of life (Oga et al., 2007). Limitations include recruitment from a single site and high drop-outs. Nevertheless, the study gathered data over a period of five years, so the probability of false positive results is slim.

Zhu and colleague's (2016) failure to commit further analyses is a limitation of the paper; conceivably a hierarchical linear multiple regression would have clarified the role of anxiety on quality of life. This is in contrast to their study by Wang et al., 2010, where they shared authorship and provided appropriate statistical calculations.

1.3.4.3 No Association. Two of the nine studies reported no association between anxiety or panic and asthma quality of life. Schneider et al. (2008) reported a longitudinal study that followed asthmatic participants from 46 GP practices across Germany for a year. PD was not a significant predictor for the dimensions on the AQLQ. Similarly, Wang and colleagues (2010) did not

identify an association between anxiety symptoms and quality of life. Nevertheless, when anxiety and depression were concomitant, there was a significant relationship with quality of life and this accounted for 15% of the variance.

1.3.4.4 Methodological Considerations: In terms of the samples sizes, two of the studies contained relatively large sample sizes, n = 256 (Schneider et al., 2008) and n = 168 (Wang et al., 2010). The three studies presented here are from different cultures (one from Germany and two from China). Schneider at al.'s (2009) findings are easier to generalise as they employed the PHQ to measure panic, though quantifying general anxiety was not considered. The longitudinal design of the study is advantageous; however, information on the power of the study is not reported, so the findings are disputable. Wang et al. (2010) provided power calculations, though they utilised a Chinese based measure reporting minimal information on its psychometric properties, and it is therefore difficult to generalise their findings.

Thus, so far the results have been fairly consistent. With only two of the nine studies reporting no association. This would suggest that reasonably AQLQ is affected as a result of anxiety symptoms or disorders in the asthma population.

1.3.5 The Relationship Between Control and Anxiety

The exploration of control can be assessed by various methods: a more subjective perception angle of the asthma control or through a complete objective measure, such as the GINA approach that is judged by medical professionals. The GINA approach takes into account FEV_1, patient history and physical examination (GINA, 2017).

The review identified 16 papers that identified the use of measures that quantify control of asthma. Four of these papers did not explore perception of control alongside anxiety (Ciprandi et al., 2016; De Peuter, Lemaigre, Van Diest, & den Bergh, 2008; Panek et al., 2015; Smith, Mildenhall, Nobel, Miranda, Shepstone, & Harrison, 2005) and were admitted into the review for other categories. In total, 12 of the studies explored the association between anxiety, asthma and control. Two of these studies overlapped in authorship, the implications of these will be discussed in methodological considerations (Wang et al., 2010; Zhu et al., 2016)

1.3.5.1 Significant Association. 10 of the 12 studies reported an association between control and anxiety in asthmatics. However, a shortcoming of using a cross-sectional study, which studies in this section mostly adopted, is the difficulty in determining the direction of causality. Table 4 has a list of effect sizes.

Six of the studies contained the ACT as a measure of perceived control. One of the studies distinguished groups according to controlled vs. uncontrolled management of asthma and reported anxiety to be significantly higher in the uncontrolled group (Viera, Santoro, Dracoulakis, Caetano, & Fernandes, 2011). Insufficient data were available to calculate Cohen's *d*. Avallone and colleagues (2012) reported a negative correlation between physical concern anxiety sensitivity and asthma control (r = -0.35); where there is an increase in anxiety sensitivity, there will be a reduction in perception of anxiety control. Furthermore, anxiety sensitivity accounted for 3.3% of the variance and was a significant predictor of asthma control.

Table 4

Effect sizes from Statistical Analysis between Control and Anxiety

Study	Effect Size / R^2
Avallone et al., 2012	r = -.35
Ciprandi et al., 2015	p = -.37
Di Marco et al., 2010	Insufficient data to calculate
Furgal et al., 2011	R^2= .21
Pilipenko et al., 2016	R^2= .03
Smith et al., 2005	d= 1.26
Viera et al., 2011	Insufficient data to calculate
Wang et al., 2010	R^2 = .06 / d = 1.16
Yang, et al., 2016	d = 0.88
Zhu et al., 2016	d = 0.58

The remaining four studies were grouped according to psychological diagnosis. There were studies that did not report effect sizes, this was calculated where sufficient information had been reported in the paper. The effect sizes reported indicated medium to large effects, d = 0.580 (Zhu et al., 2010), d = 0.879 (Yang, Zhao, Zhang, Shen, & Yuan, 2016), d = 1.164 (Wang et al., 2010) and p = -0.37 (Ciprandi, Schiavetti, Rindone, & Ricciardolo, 2015). Wang and colleagues (2010) explored a multiple regression model and reported that anxiety significantly accounted for 6% of variance in control.

Of the remaining four papers, three used guidelines to measure an objective measure of asthma control (one of which comprised a subjective measure alongside [Di Marco et al., 2010]), and one paper explored the locus of control in asthmatics (Furgal, Nowobilski, de Barbaro, Polczyk, & Szczeklik, 2011). Smith and colleagues (2005) reported a significant difference between poorly compliant and compliant groups, with a significantly larger number of

anxiety symptoms in the poorly controlled group. The effect was large (*d*= 1.257). Interestingly, there were numerous variables that were reported to impact on control, yet following a logistic regression only anxiety was a significant predictor of control. Similarly, somatoform and/or other anxiety disorder (*r* = 0.03) was a significant predictor of control in a recent study, though anxiety without somatoform was not a significant predictor of asthma control (Pilipenko et al., 2016). Interestingly, female gender also influenced asthma control similar to Trzcinska et al. (2013) and Di Marco et al. (2010). Di Marco et al. (2010) contained both two measures of subjective and objective measures of asthma control in their study, with both considered to be objective, however the ACT has a more subjective angle and is entirely self-reported. Both measures reported anxiety as a significant predictor of control. Interestingly, Di Marco et al. (2010) was the only study that showed greater number of well controlled asthmatics in the anxiety group, compared to depression group. Furgal et al. (2011) reported that attribution of control was located internally for men and externally for women.

Notably, irrespective of using objective or more subjective measures of quantifying asthma control, there appears to be a relationship between anxious asthmatics and poor control in comparison to asthma participants who do not suffer from any psychological difficulties.

Theoretically, fear and hypervigilance are concomitant with anxiety and this may propagate a narrative of 'uncontrolled illness' based on internal discernment, such as wheezing (Beck et al., 1985; Warwick & Salkovskis, 1990).

1.3.5.2 Methodological Considerations. Of the 10 studies reporting a relationship between anxiety and asthma control, two did not report well-defined

exclusion and inclusion criteria, influencing the generalizability of findings (Furgal et al., 2011; Smith et al., 2005). Notably, two studies reported a powered study, confirming the generalisability of the study (Di Marco et al, 2010; Wang et al., 2010).

Most of the studies provided good statistical analysis, though Yang et al. (2016) provided the least satisfactory analysis with the outcome measures; they failed to compute further analysis beyond univariate comparisons against outcome measures. Correlations and regression analysis would have provided a greater understanding of predictors and relationships. The study, did, however conduct such an analysis on their neurotransmitters against outcome measures. Two studies failed to report psychometric properties (Furgal et al., 2011; Wang et al., 2010). All the studies used participants with confirmed diagnosis, and seven studies were further confirmed using lung function assessments. A further methodological consideration is the shared authorship of two studies by Gang Wang and Yulin Ji, it appears flaws were identified from different areas of their quality assessment (Wang et al., 2010; Zhu et al, 2016). Where one study provided good statistical analysis (Wang et al., 2010) the other failed to provide appropriate statistical analysis (Zhu et al., 2016). Additionally, Zhu and colleagues (2016) recruited stable asthmatics whilst Wang and colleagues (2010) specifically recruited asthma patients with poorly controlled asthma. Moreover, there were 8 further papers to aid in the generalisability of findings as association between asthma control and anxiety.

Methodologically, caution is advised when using different methods of categorising control, such as the GINA approach and ACT. Di Marco et al. (2009) highlighted the possible discrepancies that can arise, with a middle group

of asthma control sufferers; though overall, they were similar. The study reported a group of asthma sufferers to be well controlled according to GINA and poorly controlled according to ACT, yet there was no significant difference in comparison to a group that had poor categorisation according to Gina (Di Marco et al., 2010).

1.3.5.3 No Association. Two of the 12 studies found no association between anxiety and control in asthmatics. Trzcinska and colleagues (2013) noted that perception of control was not association with anxiety status. Control appeared to be associated with gender, professional activity and habitation. Boudrea and colleagues (2015) classified asthma participants as having a diagnosis of PD or no PD; there was no difference in perception of control in those with asthma with or without a PD diagnosis. Conceivably, no association was made in quantification of control and lung function as measured by FEV^1, yet the PD group had a significantly higher number of emergency visits. The two studies indicate that lung functions do not influence how asthmatics perceive their symptoms and the way that they control their asthma

1.3.5.4 Methodological Considerations. Trzcinska and colleagues (2013) developed a study to include a multi-centre recruitment, detailed recruitment and a relatively large sample of 223 participants to their benefit. However, limited details on inclusion/exclusion criteria, procedural information and power of the study were reported, prompting doubt over the quality of the study. Boudrea and colleagues (2015) also developed and reported a well-defined recruitment, procedural study that utilised measures with good psychometric properties; however, caution is needed in the generalisability of findings. Almost

50% declined to participate in the study and so a small number of participants was recruited for it.

In summary, the role of anxiety/panic is overwhelmingly associated with control of asthma. The two studies that did not show an associated had several methodological flaws which may have hindered the analysis.

1.3.6 The Relationship between Emergency Department (ED) Visits and Anxiety

Eight studies that explored the use of ED and primary care services in relation to asthmatics with anxiety and/or panic symptoms. Of the 8 papers there was no overlap in authorship.

1.3.6.1 Significant Association. Seven of the eight papers identified various significant differences and associations. In contrast to Kullowatz et al.'s (2007) findings of non-significant association, a longitudinal study identified panic as a significant predictor of ED visits (Schneider et al., 2007). This was further supported by four more studies (Boudreau et al., 2015; Di Marco et al., 2010; Pilipenko et al., 2016; Smith, Mitchell, Bowler, Heneghan, & Perera, 2009)). Pilipenko and colleagues (2016) identified that the occurrence of somatoform (physical symptoms) associated with anxiety predicted both ED visits and hospitalisation (unlike Kullowatz et al., 2007). Intriguingly, where there was no somatoform (physical markers), anxiety (without physical sensations) independently continued to predict ED visits, though not hospitalisation. A further notable finding was that anxious individuals were significantly more likely to use ambulance services than walk-in facilities when accessing ED services (d = 0.29; Smith et al., 2009).

Two studies identified differences in accessing urgent primary healthcare facilities in anxious asthmatic participants (Deshmukh et al., 2008; Di Marco, 2010). Deshmukh and colleagues (2008) reported those with higher levels of anxiety accessed more urgent primary care visits, though noted that anxiety was not a predictor. A third study also reported an association between illness specific panic fear and accessing primary care, concluding that a pattern of two or more visits to primary healthcare was associated with a greater association with panic (Feldman et al., 2009).

In summary, the studies report confidently the link between anxiety/panic symptoms and accessing ED services, consistent with cognitive conceptualisations of anxiety (Beck et al., 1985; Clark, 1988; Warwick & Salkovskis, 1989). Conceivably, the perceived fear of asthma symptoms, also mimicked by panic attack, activates the survival mechanisms and therefore results in accessing ED services. Furthermore, lack of association between hospitalisation and anxiety is also consistent with the theory that misinterpretation of non-existent asthma symptoms may motivate the accessing of ED services, though the lack of physical indicators prevents hospitalisation for treatment.

1.3.6.2 Methodological Considerations. Conversely, all the studies presented in this section originated from European and Western countries with well-developed healthcare systems and plausibly easier to access; it would be interesting to consider healthcare utilisation in developing countries where healthcare utility is not as well established. Despite no reporting of power, all but one study reported significant findings in ED unitisation. Furthermore, all the studies reported good recruitment criteria and all excluding one study (Schnieder

et al., 2008) contained measures of trait anxiety. Schneider and colleagues (2008) employed panic categorisation in place of anxiety symptom measurements. Two of the seven studies failed to objectively measure lung functions (Dehmukh et al., 2008; Pilipenko et al., 2016). There are issues with recruitment and participant samples that will impact on the generalisation of findings, such as homogenous samples and no control groups (Feldman et al., 2010), exclusion of territory patients from recruitment (Boudreau et al., 2015; Smith et al., 2009) and low participation response rates (Pilipenko et al., 2016).

1.3.6.3 No Association. One of the eight studies reported a non-significant association between anxiety and hospitalisation and primary care utilisation (Kullowatz et al., 2006). This would indicate that accessing healthcare is not impacted by anxiety, rather perception of symptom severity. Interestingly, two further studies identified a non-significant association between hospitalisation and anxiety and/or panic (Pilipenko et al., 2016; Schneider et al., 2007). However, they reported other significant relationships. It appears the cognitive bias in anxiety, hypervigilance (perception) of symptoms showed an association rather than overall anxiety measure.

1.3.6.4 Methodological Considerations. Caution is advised in interpreting the result, as anxiety was controlled for. The study, like most of the studies exploring healthcare utilisation, is limited by the cross-sectional and retrospective nature of the study (Kullowatz et al., 2006). However, with Schneider et al.'s (2008) longitudinal study, the non-association is strengthened. Kullowatz et al. (2007) provided recruitment procedures, though failed to report recruitment criteria. Furthermore, symptom severity was not measured by an objective lung assessment.

1.3.7 The Relationship between Lung Function and Anxiety

Seven papers were identified that explored the relationship, or lack of, between anxiety and/or panic symptoms and lung functions. There was no overlap between authorship in any publications in this area. Four of the studies identified were experimental studies, inducing bronchoconstriction through MCT or histamine provocation (Boudreau et al., 2015; De Pueter et al., 2007; Wang et al., 2010; Ritz, Trueba, Simon, & Auchus, 2014). Conceivably, the experiment was simulating bronchoconstriction. The studies in this section provided mixed reports.

1.3.7.1 Significant Association. Three studies identified changes in anxiety levels, as lung functions changed due to MCT or histamine challenge. Those with higher baseline anxiety or panic symptoms/disorders reported a greater increase in perceived symptoms as lung function reduced (Boudrea et al., 2015; De Peuter et al., 2007; Ritz et al., 2014). The findings imply that in real life breathlessness or bronchoconstriction, those with anxiety will report increased perceptions of asthma symptoms.

In line with Cognitive Behavioural Theory (CBT) the perceived symptoms of breathlessness, irrespective of changes to lung function, may impact cognition of discerning harm to self and therefore increase fear, a principle feature of anxiety.

1.3.7.2 Methodological Considerations. In respect to quality assessment, the three papers were all of experimental designs and reported similar strengths and weaknesses. De Peurter and colleagues (2007) used a sample of asthmatics who did not have good control and had difficulties in quantifying asthma severity, which will have implications for generalisability.

Laboratory bronchoconstriction has been criticised, chiefly the ecological validity, regarding to what extent the findings can be generalised to real life settings. Hypothetically being in the laboratory setting, with the presence of medical professionals, perhaps focuses participants to respiratory sensations. Plausibly, the reverse is possible; having medical professionals in sight may reduce anxiety, as they are perceived to be safe. Furthermore, a reduction in respiratory functions is planned and not sudden, which feasibly reduces the uncertainty that anxious participants will find intolerable. Intolerance to uncertainty is another mechanism of anxiety.

1.3.7.3 No Association. Four papers highlighted no significant differences in lung function linked to perception of breathlessness or dyspnea (Ciprandi, Schiavetti, Rindone, &Ricciardo, 2015; Di Marco et al., 20; Oga et al., 2007; Wang et al., 2010). Interestingly, though there were no differences in lung function, there were differences in perception of control between anxious asthmatic vs. control (Ciprandi et al., 2015). Similar discordance has been reported with increased symptom perception (AQLQ), yet no change in lung functioning (Wang et al., 2010). Regression analysis reported no significant independent effects of anxiety on airway hyper responsiveness, though anxiety was related to negative mood states (Wang et al., 2010).

Additionally, anxiety has been reported to impact subjective and objective control and healthcare utilisation, yet lung functions do not differ (Di Marco et al, 2009); though there is an association between lung function and control. The discordance plausibly highlights the role of anxiety

1.3.7.4 Methodological Considerations. All five studies reported clear inclusion and exclusion criteria, with few of the studies confirming beyond

physician diagnosis of asthma by using MCT (Boudrea et al., 2015; Wang et al., 2010). All provided a rationale for statistical analysis and accounted for confounding variables, such as gender and age differences in groups. Only two of the studies provided power calculations and reported that they had been met (Boudrea et al., 2015; Wang et al., 2010).

This lung function is complicated, there appears to be more consistent link between breathlessness and anxiety instead of lung function and breathlessness. Experimentally inducing bronchoconstriction was found to be associated with perception of breathlessness, though, breathlessness is also reported when there is no change to lung function. There is a common theme of anxiety associated with perception of breathlessness.

1.3.8 The Relationship between Perception of Symptoms and Anxiety

Perception of symptoms is a cornerstone of asthma treatment, only five studies reported subjective perception of symptoms, during reduced lung function (Ciprandi et al., 2016), measured across five years (Oga et al., 2007), or during an asthma attack using the Asthma Symptom Checklist (ASC; De Pueter et al., 2007, Deshmukh et al., 2008; Feldman et al., 2010). All reported that increased anxiety or panic was associated with increased perception of asthma related symptoms. Furthermore, there was no overlap in authorship between any of the publications in this section.

Feldman and colleagues (2010) also postulated symptom perception as a mediator for the quality of life and anxiety.

1.3.8.1 Methodological Considerations. Irrespective of dissimilar use of validated measures, VAS to SGRQ, all studies reported similar trends. Some of the studies measured a specific symptom whilst other measured range of

symptoms. The studies produced similar results in their quality assessment (Appendix B). They all reported clear inclusion and exclusion criteria, and only Deshmukh et al. (2008), reported the study being sufficiently powered.

1.3.9 The Relationship between Dyspnea and Anxiety

Dyspnea is a cardinal symptoms of asthma, defined as the perception of bronchoconstriction or breathlessness (Lavietes, 2015). A multifaceted concept, a distinction has been made between emotional and physical sensations (De Peuter et al., 2007). Dyspnea and breathlessness will be used according to the reporting language used in the publications, nevertheless, they represent the same thing. This review identified six papers exploring the role of dyspnea and anxiety, all reporting an association. Only two of these papers overlapped in authorships, with three out of four authors overlapping across the two papers. The implications of which will be further discussed in methodological considerations (De Pueter et al., 2007; 2008).

1.3.9.1 Significant Association. The study reported discordance between perceptions of dyspnea and objective measures of lung function, yet there was an association with anxiety and catastrophic thinking (De Peuter et al., 2007). The affective aspect of dyspnea was significantly associated with anxiety (state). (r = 0.55) and the sensory aspect was associated with catastrophic thinking (r = 0.51). Interestingly, catastrophic thinking is a salient feature of anxiety and therefore a sensory aspect of dyspnea was associated with trait anxiety. Furthermore, the participants with higher trait anxiety reported increasing levels of dyspnea with decreasing lung function. In a real life setting, participants with anxiety may discern initial symptoms as catastrophic, thus setting off a sequence of survival behaviours.

Similarly, De Pueter and colleagues (2008) reported increased catastrophic thinking during induced bronchoconstriction in a laboratory setting and reported higher breathlessness. Their laboratory findings corresponded with retrospective accounts of catastrophic cognitions during exacerbations. Catastrophic thinking, a principal feature of anxiety, is reported to be associated with over perception of symptoms of dyspnea and obstruction. Further support for state (r= 0.35) and trait (r= 0.36) anxiety as a predictor for dyspnea, reported medium effect sizes (Nowobilski et al., 2009; Boudreau et al., 2015).

The association was further explored with respect to locus of control and identified differences in the anxiety and dyspnea link (Furgal et al., 2011). This highlighted that those with a strong sense of agency (internal sense of control) reported higher levels of anxiety and dyspnea than those with a weak sense of agency.

Contrastingly, dyspnea was reported to be negatively associated with lung function (r=-0.47; Lavietes, 2015). Nevertheless, anxiety continued to be a significant (and only) predictor of dyspnea (r^2=0.11).

In summary, there appears to be discordance between physical markers of bronchoconstriction and perceived dyspnea. The hypersensitivity to sensations of breathlessness indicates the role of fear, anxiety and/or catastrophising; perhaps hypervigilance influences engagement in healthcare utilisation and perhaps overmedication as well (Boudreau et al., 2015).

1.3.9.2 Methodological Considerations. Appraisal of the studies revealed mixed quality. Two studies presented in this section were investigated by Steven De Peuter as first author, with 3 other authors overlapping on both papers (De Peuter et al., 2007;2008). Both studies held differences in their

reporting of recruitment and procedures. Furthermore, where both studies measured state anxiety, only De Pueter and colleagues (2007) included a measure of trait anxiety.

Three of the studies reported recruitment criteria, giving a clearer indication to generalise findings (Boudreau et al., 2015; De Peuter et al., 2007; Lavietes, 2015). While two of the studies may have low participation rates and small samples, the strength of the studies was in using only participants who had confirmed diagnosis beyond physician diagnosis by using the MCT challenge (Boudreau et al., 2015; De Peuter et al., 2007) or Spirometry (Lavietes, 2015). De Pueter and colleagues (2008) combined the findings of three different studies; the merit in this is the use of different sites and a more representative sample. However, confounding variables of multiple procedures and testing environment conceivably impacted findings and generalizability. Furthermore, the study used mild to moderate asthmatics may be considered a limitation of the study. However, for this review, it is an advantage as all the studies used a similar sample of participants.

Finally, caution is advised in terms of causality. Given the studies adopted an experimental and cross-sectional design, one cannot conclude directionality in causality, rather a link and description.

1.4 Discussion

This narrative review summarised the existing evidence base from empirical studies on the link between anxiety and asthma, and the impact that this relationship has had on outcome measures from 2004 to the end of 2016. The narrative review was categorised according to the themes that emerged from the literature search: quality of life, control, healthcare use, lung function, perception

of symptoms and dyspnea. There is substantial evidence to demonstrate the association between anxiety and asthma has in these areas, irrespective of demographic data and spirometry results.

Two studies indicated that co-morbid anxiety has no impact on quality of life. The studies that highlighted the link contained lower levels of anxiety or used only a measure of panic, a variant of anxiety, not anxiety symptoms that other studies used (Schneider et al., 2008). There was consensus that increasing anxiety symptoms there was a decrease in overall quality of life, decrease in activity limitation, increase in symptomology and emotions. However, environmental stimuli subscale revealed to not be impacted by anxiety.

Control is a precarious concept when evaluated with anxiety, the majority of the studies in this review have shown poorer control to be significantly associated with increased anxiety, although some do not find supportive evidence (Boudrea et al., 2015; Trzcinska et al., 2013). The significantly associated papers highlighted either a negative association with anxiety disorders or symptoms, or elevated number of anxious asthmatics in the 'uncontrolled' category. Though, there were two papers in this review to indicate that anxiety can initiate better control (Di Marco et al., 2010; Furgal et al., 2011).

The review then went onto highlight the impact comorbid anxiety has on healthcare utilisation, with a theme of increasing access to emergency department and yet not association with hospitalisation. Perhaps, heightened sense of symptoms may propagate a visit to the ED and there may not be any physical problems.

Research articles on lung function and perceived symptoms, control or anxiety continued to highlight the discordance. However, three papers reported

an association, though they were all experimental studies where participants would have an expectation of reduced lung function as lung function was physically reduced. Studies in this category highlighted the role of anxiety in perception of breathlessness, rather than lung function.

Symptom perception can be breathlessness, coughing, chest tightness, etc.. Studies reported a positive association between increasing anxiety/panic related symptoms and symptom perception. This also further highlighted in the dyspnea, breathlessness, to be associated with anxiety.

The significant associations with outcome variable and anxiety, perception of symptoms or breathlessness yet normal lung function leaves the question of *how* attention modulates this relationship; perhaps mechanisms of anxiety can explain this relationship. The underlying mechanisms in asthmatics have been explored by two studies; selective attention and avoidance predicted the severity of asthma (Alexeeva & Martin, abstract only) and greater activity in the mid-insula and perigenual anterior cingulate (Rosenkranz et al., 2016). Neither explored anxiety related processes exclusively.

This review has built on the previous review by Katon et al. (2004) notably, exploring beyond the prevalence of anxiety in asthmatic and comorbid respiratory diseases. The current review has further highlighted the wide ranging impact of anxiety on asthmatic.

1.4.1 Theoretical Considerations

There are instances in which the relationship between anxiety and control was reported to be non-significant, for which there are several explanations. It is plausible that the non-significant relationship may be explained by hyper-vigilance. In the context of the hypochondriasis model, checking and the

perception of symptoms increase, which, in turn, promotes an increase in medication and better medication and consequently better control (Warwick and Salkovski, 1990).

The theory also accounts for the high prevalence of anxious asthmatics' use of emergency departments, as they begin to catastrophize minute symptoms when lung functions appear to be normal.

On the one hand, the higher prevalence of anxiety among patients with poor asthma control might promote low mood, highlighted by several studies on depression and control, though not accounted for by this current review (Deshmukh et al., 2008). The low mood, in turn, might increase perceived symptoms in such patients, thereby reducing their perception of asthma control. Furthermore, it is plausible that anxiety reduces their emotional functioning; hypothetically, the attentional resources would be occupied with threat, and therefore would neglect to deal with their disease (Mogg and Bradley, 2016). The lack of control conceivably leads to a limitation of activity and therefore a reflection of the lower quality of life.

1.4.2 Critical Consideration of the Review

The review systematically identified articles from numerous sources, with detailed inclusion and exclusion criteria. The review contained studies only with physician diagnosed or spirometry confirmed asthma sufferers, not self-reported asthma sufferers. Furthermore, all the studies contained at least one validated outcome measure to ensure validity and reliability of findings. Additionally, the review only included studies with adult samples, not adolescents or older adults. By including adolescents, the sample may have complicated the issues of control, as adolescents are not autonomous at that stage of life and the review would have

needed to have considered parental roles. Older adult samples tend to include more severe cases, thereby leading to issues with generalizability (Kullowatz et al., 2006). Furthermore, there are a greater number of co-morbid physical health and cognitive dysfunctional processes. The review included studies predominantly using the HADS as a measure of anxiety (subscale), which has excellent properties. Although there were different measures of anxiety, they were all validated. Lastly, the review only included studies that were published in peer-reviewed journals. This may draw criticism for publication bias, yet the studies included are of good quality and have been through a rigorous process prior to publication.

The review was not without limitations. There was no differentiation between the inclusions of studies that utilised self-reported data instead of the gold standard face-to-face interviews. Self-report questionnaires feasibly represent the majority of the studies, which may be subject to recall bias and, therefore, caution is advised. However, given that the review considered 26 studies, it would seem unlikely that most participants experienced recall bias and misconstrued their perceptions to create an association between co-morbid anxiety and the outcomes. Furthermore, the questionnaires included in this review held some kind of validity and reliability, although not all provided psychometric properties.

Some studies only used one site for recruitment, which can be considered a limitation. However, the narrative review permits the generalizability of the findings, as the studies collectively drew participants from multiple centres and countries across the world, with at least one study from each continent. Irrespective of cultural identity, the relationship is evident.

Most studies used cross-sectional designs and therefore cannot be used to identify the causative link. It remains unclear from this review whether asthma causes anxiety or anxiety undermines disease control. The cognitive processes or mechanisms of this relationship remain to be elucidated. However, this review has included four experimental studies that enabled the validity of detecting anxiety during experimental bronchoconstriction (Boudrea et al., 2015; De Pueter et al., 2007; De Pueter et al., 2008; Ritz et al., 2014). The experimental studies gave an opportunity to measure decreased lung function an explore dyspnea and symptom perception.

Additionally, the review is based on the reporting of published studies rather than the actual quality of the studies; there may have been many other analyses or measures used in the studies, though not reported. The studies did not all present confidence intervals, so these were not reported in this review.

Finally, several publications in some sections of the review (quality of life, asthma control and dyspnea) shared authorship which could potentially be considered a limitation in terms of generalising findings. However, in their respective section they were two papers amongst further 4 to 8 independent publications all reporting similar findings and therefore no significant implication to the review.

1.4.3 Clinical Implications

The National Institute for Health and Care Excellence (NICE) has quality standards in place for asthma care with the recommendation of improving the quality of life, measuring control, treatment for acute asthma and other physical health considerations. Surprisingly, given the association with anxiety, psychological input specifically has not been included in NICE guidelines for the

treatment of asthma. Psychological input will plausibly improve the quality of life, control and the unnecessary accessing of emergency services. It is imperative to consider the role of psychological assistance in managing asthma, which has provided for other chronic health conditions, such as diabetes (NICE, 2016). NICE recommends psychological input in the management of diabetes care for psychological difficulties and/or adherence to care plans.

A multidimensional integrative approach, with the inclusion of psychological care, may reduce the unnecessary accessing of emergency services (Schneider et al., 2008). Furthermore, including a basic anxiety related self-report questionnaire in assessing psychological status during consultation with patients would plausibly aid in consideration of treatment options in addition to pharmacological care.

1.4.4 Future Directions

There was also a further association of anxiety and dyspnea/breathlessness, which is not surprising given that perception of breathlessness is an anxiety related process in asthmatics and also the cornerstone of asthma care. The relationships have been continually demonstrated, though little is known of the mechanisms that impact on suboptimal control and quality of life. Better identification will enable better targeting of behaviours using a tailored psychological therapy that currently does not exist for comorbid anxiety in asthmatics. Identification of processes will further enable the development of effective strategies for managing co-morbid anxiety.

Chapter 2: Empirical Paper. Using the methacholine challenge to determine how psychological mechanisms impact asthma symptom perception and quality of life.

2.1 Introduction

Asthma affects over 338 million people globally (Global Asthma Network; GAN, 2014). Asthma is defined as a respiratory disease that is characterized by obstruction of the airway during an episode. Symptoms include the inability to breathe easily, chest tightness, wheezing, and coughing (Martinez & Vercelli, 2013). Chronic airway inflammation is associated with compromised lung function.

Despite optimal treatment options, poor outcomes have consistently been reported (Demoly, Gueron, Annunziata, Adamek, & Walters, 2010). Numerous factors are responsible for inadequate symptom control, including psychological distress (e.g. anxiety; Thomas, Bruton, Moffatt & Cleland, 2011). The impact of asthma transpires in diverse ways, such as low income (inability to work), sleep problems, avoidance of exercise, specific dietary requirements, difficult pregnancies, lower quality of life, and, in severe cases, death (Scottish Intercollegiate Guidelines Network [SIGN], 2014). Essentially an understanding is needed of the neurocognitive and behavioural mechanisms to aid in the development of appropriate therapies to complement the current pharmacological interventions in asthma management (Edwards et al., 2017).

2.1.1 The Role of Anxiety and Symptom Perception in Asthma

2.1.1.1 Anxiety. Anxiety is characterized by feelings of excessive fear, worry, and distress (Bishop, 2007), arising from dysfunctional interpretation of events based on irrational beliefs and cognitive bias (Bishop, 2007; Wells, 1997). Literature has consistently reported strong associations between anxiety and asthma (Cordina, Fenech, Vassallo & Cacciottolo, 2009; Katon, Richardson, Lozano & McCauley, 2002; Thomas et al., 2011), anxiety-related

correlations with symptom perception (Deshmukh, Toelle, Usherwood, O'Grady & Jenkins, 2008), and the impact anxiety has on compromising outcomes.

A review of the literature suggests that anxiety disorders negatively affect self-care, self-efficacy, and functioning in people with asthma and hence adversely influence medical costs for asthmatics (Katon et al., 2002). There appears to be a positive association between increasing anxiety and increasing use of medication despite normal lung function (Cordina et al., 2009).

2.1.1.2 Perception of Symptoms. Published studies have highlighted the relationship between anxiety and asthma, to be associated with poor asthma symptom outcome and poorer health status (Deshmukh et al., 2007). Expectedly, perception of symptoms, namely breathlessness, is also a process of anxiety. Research has highlighted the perception of symptoms as being either blunted or overperceived, as well as ambiguity in a situation and mental representation of previous experience of episodes negatively influencing quality of life and optimal management of asthma control, irrespective of sensory input (Janssens, Verleden, De Peuter, Petersen & Bergh, 2012).

Anxiety heightens the perception of respiratory fluctuations irrespective of physiological changes such as lung function (Di Marco et al., 2010; Katon, Lin & Kroenke, 2007). Di Marco et al. (2010) reported a negative association between over-perception of symptoms and decreasing control of asthma. Janssens et al. (2012) further reported the link between control and symptom perception, with increased perception of symptoms associated with poorer control. Unexpectedly, there was also an association between reporting perceived increase in symptoms and increased physical activity. It appears perception of symptoms has assorted impacts on outcome variables. Additionally, Feldman et al. (2010) reported symptom perception as a mediator for quality of life

Dyspnea, the subjective discernment of breathlessness, is a variant of symptom perception. Expectedly, anxiety has also been strongly associated with increasing symptoms of anxiety and increased perception of symptoms of breathlessness (De Pueter et al., 2007, Deshmukh et al., 2008; Feldman et al., 20). Furthermore, anxiety is a predictor of dyspnea (Laviete, 2015).

With regards to cognitive behavioural therapy (CBT), researchers have reported diverse outcomes, describing modest efficacy (Hofmann, Asnaani, Vonk, Sawyer & Fang, 2012), inconclusive results (York, Fleming & Shuldham, 2007), and some success (York, Fleming, Shuldham, Rao & Smith, 2015). Tailored therapeutic interventions have yet to be developed despite the link between asthma and comorbid anxiety. Conceivably, further clarification of the relationship with perception of breathlessness in relation to outcome variables on quality of life and control of asthma is needed.

2.1.2 Models of Anxiety and Symptom Perception

Pertinent psychological processes that contribute to and maintain anxiety include perception, motivation, memory, attention, and motivation (Wells, 1997). These processes are interrelated and challenging to disentangle, as they predominantly co-exist or overlap with processes. For instance, when an asthma sufferer is experiencing a reduction in lung function or bronchoconstriction, they may develop a perception (a psychological process) of the symptoms, whether they are threatening or not. Cognitive resources drive the development of perception, such as attention to or focus on the symptom (another psychological process). The following describes the theoretical underpinnings of anxiety and perception of symptoms.

2.1.2.1 Anxiety. Anxiety is driven by fear, and appraisal of it is multi-faceted with multiple models of anxiety attempting to provide a theoretical understanding. One model in particular is the cognitive motivational view of the mechanisms underlying cognitive bias.

This view proposes that anxiety is determined by the lower appraisal of a threat and that this vulnerability factor in anxiety motivates attentional deployment (Mogg & Bradley, 1998). There are two functional systems; valence evaluation is the appraisal of the threat phase and goal engagement involves directing behaviour towards external stimuli that are motivationally salient. In anxiety, once the appraisal of stimuli is deemed threatening, innocuous stimuli are assigned a high threat value, subsequently deploying attentional resources to that stimuli. The preconscious process is involved in orienting visual inspection for threatening stimuli. Those with higher levels of anxiety will evaluate non-threatening stimuli as more ominous than individuals with milder anxiety symptoms.

The relationship between valence-evaluation system and the goals engagement system is plausibly non-linear. Stimuli that are not appraised as ominous would mean no attentional bias. However, when the threat value of stimuli is mild and there are low threat levels, attentional resources are plausibly directed away and a goal-orientated focus is not maintained (MacLeod et al., 1986; Mogg et al., 2000)

Attentional bias to threat is one way of understanding the underlying neurocognitive mechanisms of anxiety, which provide cause for and maintain anxiety. The attentional control theory (ACT) highlights the role of hypervigilance, poor attentional control, and selective orientation to threat. ACT posits that competition for attentional resources is dependent upon bottom-up sensory processes and top-down control processes (Eysenck, Derakshan, Santos, & Calvo, 2007; Bishop & Froster, 2013). The bottom-up process prioritizes stimuli based on conspicuous features (e.g., stimulus valence, which is the extent to which it is a threat or reward). The top-down control process is from prefrontal control mechanisms that prioritize the stimuli (Bishop, 2008). The two mechanisms determine the output to response and memory systems.

With anxiety, there is increased attentional bias towards negative valence stimuli, indicated by slower or error-laden processing of neutral valence stimuli in the midst of threatening distractors. Therefore, it may be that asthmatics with higher anxiety symptoms will selectively attune to bodily symptoms that are appraised as threatening in the midst of other non-symptom information that suggests there is no impending asthma attack. In essence, the competition between threat valence distractor stimuli versus the presence of task-relevant stimuli in capturing attentional resources is modulated by the threat level according to amygdala and the prefrontal control mechanism. Furthermore, ACT distinguishes between the overall *effectiveness* of performance and the *efficiency* utilized (Eysenck et al., 2007). This means that anxious individuals can present as effective in their cognitive performance at the expense of efficiency. As more demand is placed on attention, effectiveness begins to reduce. Research has reported variability in selective attention to threats across individuals (Bishop, 2007; 2008).

2.1.2.2 Perception of Symptoms. Incongruence between reported asthma symptoms and pulmonary function has been repeatedly reported in clinical settings and illustrated in research. Perception of asthma is divided into groups of either over- or under-perceivers; this was traditionally thought to be a one-dimensional trait like anxiety (Janssens, Verleden, De Peuter, Van Diest, & Van den Bergh, 2009). Janssens et al. (2009) proposed an alternative model of the perception of symptoms as not stationary and able to move between both conditions. It has been hypothesised that perception of symptoms can be influenced by sensory, contextual, emotional, and personality variables. The model explains why perception of symptoms may evoke symptoms without bronchoconstriction (Put et al., 2004). The model also proposes negative effects as associative cues, which are learned from previous experience of exacerbation to be associated with negative effects; therefore, the presence of a negative effect may trigger the perception of an increase in symptoms (Put et al., 2004). This

is in line with classical conditioning, or learned fear associated with an experience rather than an object.

One of the key mechanisms of this model is attentional disposition. Exploring contextual factors (e.g. bronchoconstriction or bronchodilation) influences attentional process that drives symptom perception and/or trait anxiety. Furthermore, inhibitory responses are hypothetically compromised in this study in that potential threat reduces inhibitory responses or executive control, leading to inflexibility of managing asthma symptoms and thus disengagement from asthma symptoms (Thayer & Lane, 2000). See Figure 3 for an illustration of the processes involved in symptom perception.

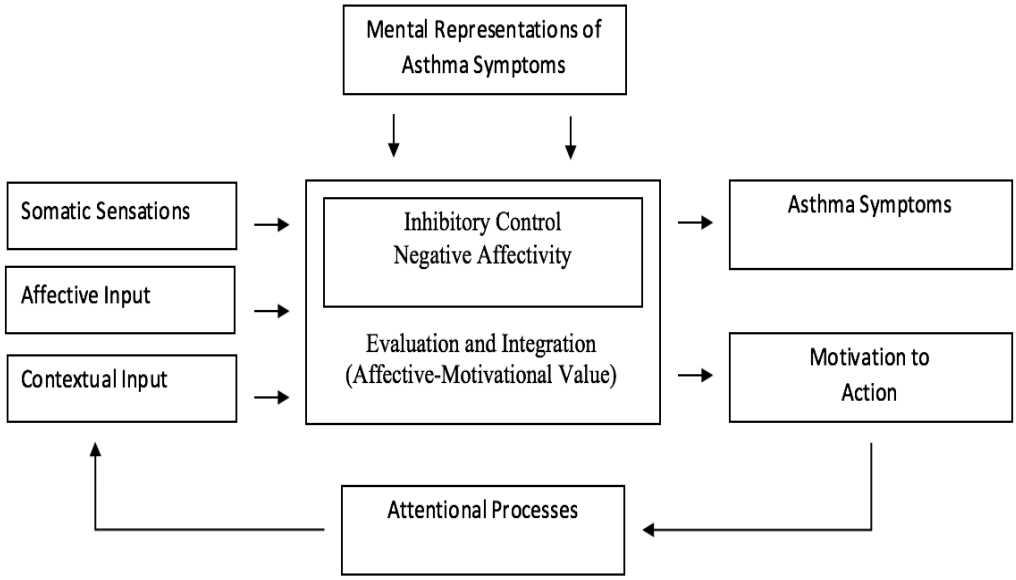


Figure 3. Illustration of symptom perception (adapted from Janssens et al., 2009)

The model posits a multi-dimensional perspective on the perception of asthma and thus plausibly identifies predictors of symptom perception. The role of attentional bias in this model influences perception of symptoms. Treatments are available that target attentional bias, directing attention away from the threat (Mathews & McLeod, 2002) and/or attending to sensory features of pain in an effort to disregard the affective features (Morley, Shapiro, &

Biggs, 2004). Brain processing has been shown to underlie symptom perception, specifically to influence affective and aversive sensations such as breathlessness (von Leupoldt et al., 2009).

In support of the model, an experimental study was adopted to induce bronchoconstriction, a useful medium to assess accuracy of symptom perception (Janssens et al., 2012). It was found that during negative affects and higher symptom perception at baseline and during an ambiguous period that bronchoconstriction was a predictor of poorer asthma control and lower quality of life. Per the literature, pulmonary function was not a predictor.

2.1.3 The Role of Attention

Attention has been operationalized as three systems: alerting, orienting, and executive attention (Dennis, Chen, & McCandliss, 2008; Posner & Peterson, 1990). Alerting is the system responsible for activating and preserving awareness. Orienting reflects the organization of attentional resources towards chosen channels of information and mitigates spatial attention; this is tantamount to the bottom-up process in the bias competition model. Executive attention exemplifies higher-level processing, such as resolving conflict when there is competition from various sources for attentional resources. The attention network test (ANT) combines the three attention systems into a single assessment (Dennis et al., 2008; Fan, McCandliss, Sommer, Raz & Posner, 2002).

To date, limited studies have explored the role of attentional dysfunction, a process of anxiety in asthmatics, which may underlie the psychological (threat) and physiological aspects of asthma. Attentional dysfunction conceivably explains the discord between lung function and symptom perception that is often reported (Banzett, Dempsey, O'Donnell & Wamboldt, 2000; Lehrer et al., 2002).

Attentional studies in asthma have so far demonstrated swifter processing of asthma-related cues during a test of interference and reaction time, namely the Stroop task (Rosenkranz, Busse, Sheridan, Crisafi, & Davidson, 2012). Futhermore, a published abstract also highlighted the role of selective attention to threatening stimuli in predicting asthma symptom severity (Alexeeva & Martin, 2013).

In addition to attentional processes of anxiety explored in this study, perception is a further psychological process that will be explored, as research has continually demonstrated that perceived breathlessness is linked to anxiety during experimentally induced bronchoconstriction (Spinhoven, van Peski-Oosterbaan, Van der Does, Willems, & Sterk, 1997) and predicted control and quality of life (Janssens et al., 2012). It would thus be of interest to investigate the role of percieved breathlessness during experimentally induced bronchoconstriction and the relationship it has with quality of life and control as the above studies have demontrated. This study will further explore whether anxiety-related cognitve processes of attention are predictive of symptom perception.

2.1.4 Tools Measuring Attention

Previously, studies measuring attention have used the Stroop task, a tool also utilized in anxiety research to measure attentional bias. The tool has been modified to test for unintentional processing of threat-related information (Mogg, Mathews & Weinman, 1989; Wells, 1997). The study reported higher levels of dyspnea (laboured breathing) in more anxious patients. Furthermore, dyspnea correlated highly with emotionally threatening stimuli, and participants in the more severe asthma group were faster to read threatening words (Martińez-Moragón. Perpiña, Belloch, Diego & Martińez-Moragón, 2003).

A functional magnetic resonance imaging (fMRI) study adopted the Stroop task and noted all participants responded faster to asthma-related cues than in neutral tasks (Rosenkranz et al, 2012).

The dot-probe task is a filtering task requiring the participant to attend to a scene whilst disregarding an alternative scene. The dot probe task is regularly adapted, using words that have been judged threatening for sample groups. Studies have reported that anxious participants tend to focus attention on threat words, whereas control participants shift their attention away from threat words (Mogg, Matthews & Eysenck, 1992).

Finally, the ANT, a relatively recent development in measuring attentional processes, is a computerized task that is extensively used in measuring alerting, orienting, and executive functioning (Ainsworth, Eddershaw, Meron, Baldwin & Garner, 2010; Fan et al.,2002; Garner, Attwood, Baldwin & Munafò, 2011). It has been experimentally demonstrated to elicit increases in alerting and orienting attentional processes in relation to anxiety or emotional processes of hyper-vigilance although no change in executive function was found (Garner et al., 2012).

2.1.5 Methacholine Challenge Test (MCT)

MCT is a standardized challenge that causes bronchoconstriction in individuals inhaling a drug called methacholine (Rubinfeld & Pain, 1976). The process of bronchoconstriction during the challenge, causes airways to contract involuntarily and narrowing the airways in asthmatics to assist in diagnosis. MCT reduces lung function to 80%. MCT has also been used in experimental studies to exacerbate symptoms in asthmatics in order to get close to the reality of sufferers and measure perception and psychological difficulty (Boudreau et al., 2015). Boudreau et al. (2015) induced bronchoconstriction and found anxious asthmatics reported higher levels of distress and catastrophization of symptoms. There have been reports that there is no relationship between MCT and perception of the lung functioning, which is surprising as hypo-perceivers among severe asthmatics tend to be sensitive to lung functioning (Chetta, Foresi, Marangio, & Olivieri, 2005), including adults who perceived fewer symptoms during MCT (Killian Watson, Otis,

Amand, & O'Bryrne, 2000). Interestingly, in a study on children, MCT revealed no link between anxiety and symptom perception, though in mild asthmatics heightened symptom perception positively correlated with higher trait anxiety (Chen, Hermann, Rogers, Oliver-Welker & Strunk, 2006). Contrastingly, a further study highlighted the link between heightened anxiety and symptom perception during experimental bronchoconstriction (Spinhoevn et al., 1997).

2.1.6 Aims of the Study

Research is necessary to examine the cognitive processes in individuals with asthma. It is predicted that attention will become impaired during laboratory-induced bronchoconstriction and linked to physiological markers of asthma such as breathlessness and psychological effects in order to inform psychological interventions that target specific processes to improve asthma care.

Hypotheses:

1. Does perceived breathlessness change when anxious during bronchoconstriction and bronchodilation? It is predicted physical changes in lung functioning (bronchoconstriction and bronchodilation) will be associated with perceived breathlessness and increasing anxiety.

2. Does anxiety or lung function predict perceived breathlessness? It is predicted that perceived breathlessness will be predicted by state anxiety and not lung function.

3. Do anxiety and perception of symptoms (breathlessness) predict quality of life, control, and healthcare utilisation? It is predicted that increased anxiety and perceived breathlessness will increase access and utilisation of healthcare. Furthermore,

increased anxiety and perceived breathlessness will be associated with lower quality of life and asthma control.

4. Does perceived breathlessness correlate with reduced attention control, as measured by the computerized ANT? Reduced attention control is purported to be one mechanism underlying dysfunctional cognitive biases in anxiety. We hypothesize that participants demonstrating increased perception of asthma symptoms will show reduced attention control. With particular reduction in executive control, as breathlessness increases (as anxiety is associated with breathlessness, research has highlighted an increase in anxiety is associated with a reduction in executive control, Pacheco-Unguetti, Acosta, Callejas, & Lupianez., 2010).

2.2 Methods

2.2.1 Design

The study is a repeated measures experimental design. The predictor variables are scores measured on the trait axis of the State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, & Lushene, 1983), and perception of breathlessness as measured by the Visual Analogue Scale (VAS; Jaeschke, Singer, Gordon, & Guyatt, 1990).

The outcome or dependent variable are the scores on a battery of tests: lung function, state anxiety (STAI; Speilberger et al., 1983); Standardised Asthma Quality of Life (AQLQ[S]); Juniper, Buist, Cox, Ferrie, & King, 1999); Asthma Control Questionnaire (ACQ; Juniper, Guyatt, Cox, Ferrie, & King, 1999); the Attention Control Scale (ACS; Derryberry & Reed, 2002); and scores on a computerised attentional task (ANT; Fan et al., 2002).

The cognitive and emotional processing outcome measures will be administered during bronchoconstriction and bronchodilation in the order illustrated in Figure 4.

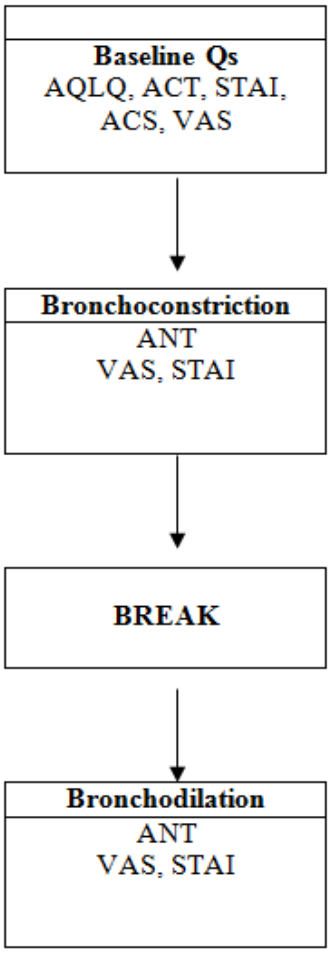


Figure 4. Design of Study

2.2.2 Participants

Recruitment took place at a local hospital and university in the south of England. Participants responded to advertisement via email or telephone, and potential participants were given an information sheet and then screened for eligibility (See Appendix C for recruitment poster; Appendix D for participant information sheet). Participants were also recruited from the asthma volunteer database at the hospital.

Participants were reimbursed for travel expenses and time dedicated to the study up to £50. The study was funded by NIHR Southampton Respiratory Biomedical Research Unit.

The recruitment process is illustrated in Figure 5 using a flowchart of 81 potential participants to complete recruitment.

The recruitment criteria specified the inclusion of participants who have a diagnosis of asthma, understand written and spoken English, and have the intellectual ability to understand and follow the study instructions. BTS/SIGN asthma guidelines treatment steps 2/3 and 4/5 were employed to determine suitability of asthmatics taking part in the study. This involved measuring FEV_1%, airway responsiveness, or diurnal variation in PEF.

The study excluded participants who were being treated with steroids, had a history of significant mental health disorders not related to anxiety or depression, significant comorbidity, had a diagnosis of cancer in the last five years, were unable to provide written consent, or were pregnant or breast feeding (see Appendix E for Consent Form). Additionally, participants were removed from the study if they had difficult asthma as stipulated by the British Guidelines on Asthma Management (SIGN, 2016) or if their spirometry tests reported FEV_1 below 70%, as the risk during bronchoconstriction is higher.

Power calculations were conducted using G*Power (Faul, Erdfelder, Lang, & Buchner, 2007). Based on previous research on attentional network (Garner et al., 2011), effect size of r=.43 was set as correlation pH1, .80 power, and 5% significance calculated a sample size of 40 to power the study. The study consists of 34 adult participants; however, due to discontinuation related to lung function assessment, the study contains data from 31 participants. The remaining data from the three discontinued participants was included with their permission. Participants were recruited between November 2016 and March 2017.

Sample size of 31 for regression analysis using two predictors is powered at .99, using the effect size of f^2= .75 (determined by G*Power using effect sizes provided by Garner et al, 2011).

The 34 participants were a combination of students and normal civilians with a diagnosis of asthma. The majority of participants were females (*n*= 21; 61.8%) who were not currently smokers (58.9%), of which 11.8% were ex-smokers. The age of participants ranged from 19 to 73, with a mean of 34.94 years (SD 14.66).

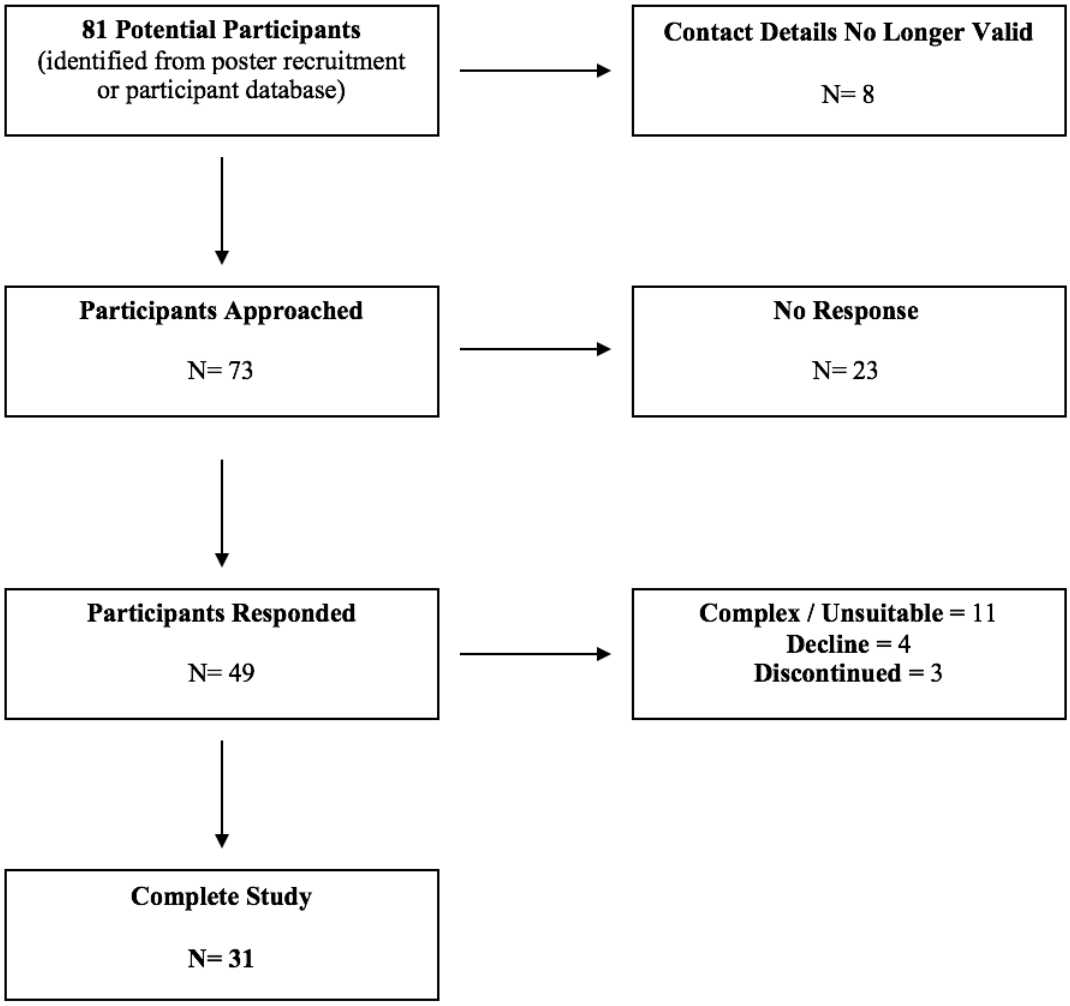


Figure 5. Flowchart of the recruitment process, with an initial 81 potential participants.

2.2.3 Materials and Procedure

The study utilised several measures during various stages of the experimental design, some of which were repeated to capture pre, during, and post MCT as outlined in Figure 4 above.

2.2.3.1 The State-Trait Anxiety Inventory (STAI). The 40-item self-reported questionnaire quantifies two concepts of anxiety: State (S-Anxiety) and Trait (T-Anxiety) (Spielberger, Gorusch, Lushene, Vagg & Jacobs, 1983). The S-Anxiety scale measures situation specific anxiety, a temporary condition. S-Anxiety includes measures of perceived tension, worry, activation/arousal, nervousness, and apprehension, a temporary state elicited for the duration of a visible perceived threat. The T-Anxiety scale measures anxiety that is generalizable to many situations and describes a personality characteristic, with variability in the presentation and duration of anxiety. Furthermore, the subscale includes additional measures that represent stable aspects of anxiety, such as calmness and security. Each subscale is represented by 20 questions, for example, '*I feel* pleasant'. Respondents rate the statement using a four-point Likert scale (0= not at all to 4= very much so). The STAI demonstrates good internal consistency and test-retest reliability (a = >.89; Gros, Antony, Simms and McCabe, 2007). The validity of the STAI is judged to be moderate as it has yet to be formally validated with the asthma population and is limited in discriminating anxiety from depression as with other anxiety measures (Kennedy, Schwab, Morris & Beldia, 2001). Higher scores reflect increased anxiety (Appendix F).

2.2.3.2 Visual Analogue Scale (VAS). The VAS is a tool designed to capture sensory information. Research has examined the extent of 'breathlessness' measures response in induced breathlessness. The VAS has been reported to show comparable responsiveness and validity in experimental and randomised control settings (Adam, Chronos, Lane, & Guz, 1985; Ainsworthet al., 2013; Jaeschke et al., 1990). Higher scores indicate higher perceived breathlessness (Appendix G).

2.2.3.3 The Standardized Asthma Quality of Life Questionnaire (AQLQ (S)). This is a 32-item self-reported questionnaire designed to measure domains of symptoms, activity limitation, emotional function, and environmental stimuli in participants with asthma

(Juniper et al., 1999). The questions are answered using a seven-point scale based on severity ratings between 7 (not impaired) and -1 (severely impaired). Items such as '*experience a feeling of chest heaviness*' are answered using this seven-point scale. The AQLQ(S) has good intraclass correlation (ICC) reliability, which indicates good reliability (ICC= 0.96) parallel to the AQLQ measure. Similarly, cross-sectional validity has been reported. Each dimension and overall score is totalled and then divided by seven, with higher scores indicating good functioning (Appendix H).

2.2.3.4 The Asthma Control Questionnaire (ACQ). This is a seven-item self-reported questionnaire is designed to measure the degree of control participants have over their asthma management (Juniper et al., 1999). The questions are rated using a seven-point scale, with 0 being controlled and 6 being severely uncontrolled. The scale has good reliability (interclass correlation coefficient =.90). The ACQ has also been validated and is reported to have strong discriminatory properties. A quantitative value of 1.5 or over is quantified as poor asthma control (Appendix I).

2.2.3.5 Borg Scale. This is a subjective scale that measures properties similar to Likert Scales, and has been used in various studies to measure feeling of bronchoconstriction (Turcotte, Corbeil, & Boulet, 1990; Wamboldt, Bihun, Szefler, & Hewitt, 2000; Appendix J)

2.2.3.6 The Attention Control Scale (ACS). This 20-item self-reported scale is designed to measure attention; initially, it was separated into attentional focusing and attentional shifting (Derryberry & Reed, 2002; Ólafsson, Smári, Guðmundsdóttir, Olafsdóttir, Harðardóttir & Einarsson, 2011). The measure focuses on capability to regulate attention in relation to negative and positive emotions. Items such as '*I can quickly switch from one task to another*' are answered using four-point scales, with 1 being almost never and 4 being always. The internal consistency on both scales is adequate (Cronbach's α=.82 for Focusing, α=.71 for Shifting) (Judah, Grant, Mills, & Lechner, 2014). Higher scores indicate greater

attentional control on the full scale. The focusing subscale indicates greater attentional focus, and the shifting subscale indicates greater capacity for attentional shifting (Appendix K).

2.2.3.7 The Attentional Network Test (ANT). This is a computer-based task measuring three aspects of attention; alerting, orienting, and executive control networks (Fan et al., 2002). The ANT provides a functional distinction of the networks in a clinical population. The ANT has high test-retest reliability, namely 0.52 for alerting, 0.61 for orienting, and 0.77 for executive control. The three constructs have no significant correlations among them; however, a study reported that alerting and orienting were significantly correlated (Fan et al., 2002). The current study found no significant correlations between any of the three networks; orienting and alerting (r=.107, *p*=.313), orienting and executive control (r=.087, *p*=.353), and alerting and executive control (r=-.120, *p*=.297).

Four cue types, namely spatial, double, centre, and no cue, and two flaker tasks (congruent and incongruent) are presented in sequence. Participants are given two options of right and left tabs on a keyboard and are expected to determine the direction of the central arrows. Stimuli are presented in a combination of flanker and cue tasks, which translates as visual images of arrows appearing above or below the fixation (+), with conditions that either encompass flankers or do not. There are variations to the ANT programme (figure 3) taken from Garner et al (2012) that illustrate the programme adopted by the current study. An example of the sequence of visual presentation that appears in the programme begins with a 400-1600 ms exposure to a fixation cross, followed by a type of cue (or no cue) for 100 ms, a 400 ms intermission, a further fixation, and then target that is presented until a choice is made by the participant. Figure 6 is an illustration of the ANT stimuli that appears on the screen.

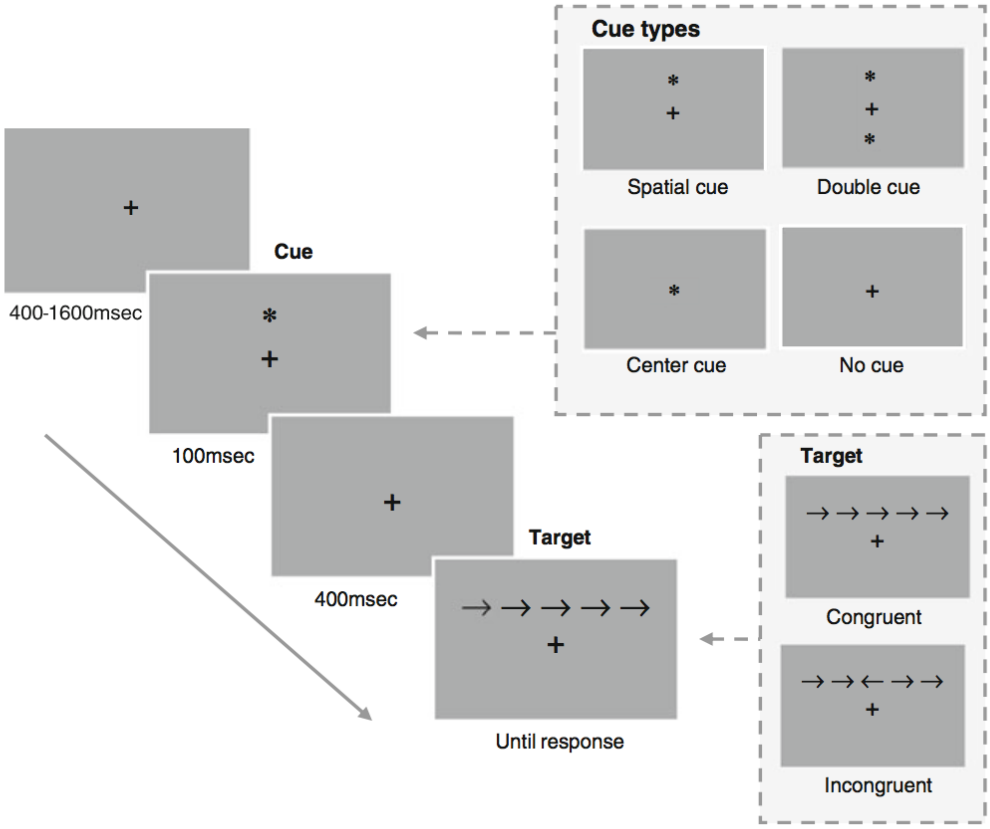


Figure 6. ANT cues and presentation of stimuli (taken from Garner at al., 2008)

Reaction times (RTs) were calculated for each participant and were consistent with previous studies (Fan et al., 2002). Following the removal of RT from incorrect trials, each network was calculated as follows: alerting (= mean RT (double cue conditions) – mean RT (no cue trials)); orienting (= mean RT (spatial cue conditions) – mean RT (centre cue trial); and executive control (=mean RT (congruent trials) – mean RT (incongruent trials). A shorter time indicates quicker orienting, alerting, and executive functioning skills. Cases were removed where there were exceptionally high standard deviations of greater than three and very low accuracy of less than 75% prior to any inferential statistical analysis. An example of a trial representing each network is in Figure 7. Alerting is measured using the reaction time from the point of warning. Orienting is measured using the variation in response time regarding where the target will occur, and executive network efficiency is measured by participant's response of clicking two keys that indicate direction during two flanker

conditions (Fan et al., 2002). Participants were given an opportunity to practise with eight randomised practise trials. The test had 64 randomised experimental trials, with 16 trials per cue type condition.

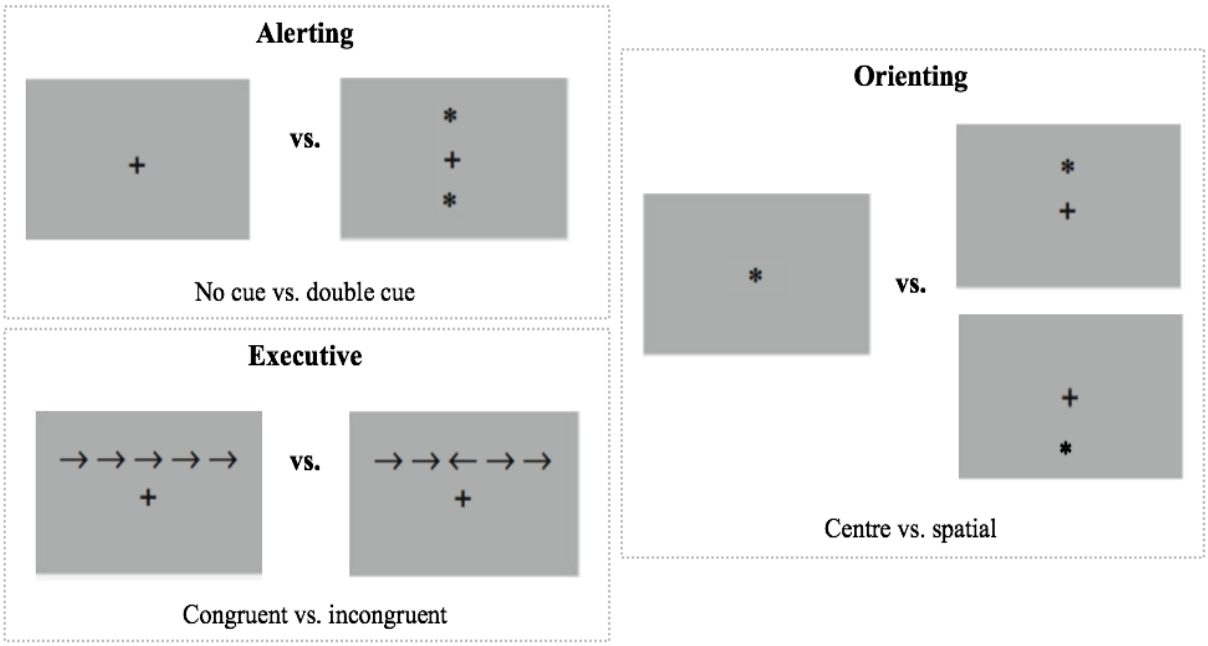


Figure 7. Illustration of ANT trial of each network.

2.2.3.8 Methacholine Test (MCT). Using the hospital guidelines for the MCT, all participants were assessed for their lung function using the spirometry to determine the baseline FEV_1. The MCT was performed using a Jaeger APS Dosimeter and Viasys Software, steered by a senior technician employed by the NHS. Once conformation of FEV_1 was greater than 70%, a 0.9% saline and 32mg/ml solution of methacholine was inhaled a nose clip until there was a reduction of 20% lung function for functioning at 80%.

2.2.3.9 Procedure. Once participants were screened, they were instructed to withhold from antihistamines and asthma medication from 48 to 8 hours, depending on the type of medication, prior to testing for the purpose of the MCT. All participant subjected to a medical examination and medical history by a medical doctor specialist in respiratory disease to ensure they were physically healthy to take part in the MCT. The experiment began with baseline measures as depicted in figure 3. Participants completed baseline questionnaires,

underwent the spirometry procedure to confirm lung function, this was led by a technician, and then administered the MCT. A second set of questionnaires and computer task delivered on a laptop were also administered. Reversibility of bronchodilation was performed by a trained research nurse using bronchodilator medication such as salbutamol to open the medium and large airways of the lungs. Lung function was assessed to ensure lung function had returned to normal and verbal debrief was given. All experiments were undertaken at the hospital.

2.2.4 Ethical Considerations

The study was approved by both the University of Southampton Ethics Committee, School of Psychology (Appendix M) and National Health Service Ethics Committee (Appendix N).

2.2.5 Statistical Analysis

Correlational analysis and regression models were used for hypothesis one to four. Paired t-test was used to compare the differences in experimental conditions and to provide further descriptive detail in the instance correlations were not supported.

Hypothesis one: Paired t-tests will confirm changes in anxiety (STAI) and breathlessness (VAS) during bronchoconstriction and bronchodilation. Changes in anxiety/breathlessness will be examined using Pearson's correlation to explore associations between perception of breathlessness (VAS) and state anxiety (STAI).

Hypothesis 2: Hierarchical; multiple regression analysis was utilised to see whether perceived breathlessness (VAS) was predicted by state anxiety (STAI) or lung functioning (bronchodilation and bronchoconstriction).

Hypothesis 3: following correlational analysis, multiple regression analysis was utilised to see whether asthma control (ACQ), asthma quality of life (AQLQ) and healthcare

utilisation (AE and GP visit) were predicted by trait anxiety (STAI) or perceived breathlessness (VAS).

Hypothesis 4: correlational analysis was utilised to see whether there was an association between attention (ACS and ANT) and perceived breathlessness (VAS) during each experimental conditions and differences of the scores to measure outcomes. Further T-tests were conducted to provide useful descriptive data on bronchoconstriction and bronchodilation condition for attention, perception of breathlessness and state anxiety.

Due to several variables not being normally distributed, all analyses were bootstrapped (Field, 2013; Efron & Tibshirani, 1993). Data was analysed using SPSS version 2.40.

2.3 Results

Most of the self-report measures were administered at three time points: baseline, bronchoconstriction, and bronchodilation. However, some of the measures were only administered during bronchoconstriction or bronchodilation. 'Difference scores' were calculated by deducting the bronchoconstriction scores from the bronchodilation scores to measure the effect on outcome measures.

2.3.1 Data Preparation

During the preparation of ANT data, one participant had a very high RT (> 3 SD) and three participants reported extremely low accuracy (< 75%), indicating that the task was not completed correctly. They were removed from further data analysis. Boxplots, histograms, and standard deviations were used to identify and remove outliers. Extreme outliers were transformed guided by a comparison with next extreme value to see the difference and then replace the extreme values with the next highest/lowest value and adding/subtracting one unit (Tabachnick & Fidell, 2014).

Shapiro-Wilk tests and visual inspections of histograms and boxplots were completed to test parametric assumptions of all variables. Shapiro-Wilk tests revealed non-significant differences for the majority of the variables, excluding the Borg baseline (W[30] = .624, $p < .001$), and bronchodilation (W[30] = .526, $p < .001$). Further skewness analysis revealed Borg at baseline was skewed ($z = 2.22$) beyond the accepted range of ± 1.96. Data transformation was calculated using logs. Bootstrapping was utilised for variables that did not meet parametric assumptions (Field, 2013).

Scatterplots did not illustrate any non-linear relationships between predictors and outcomes, though in these instances heteroscedasticity was observed. This is often caused by non-normality of a variable and such violations were managed through the use of bootstrapping (Tabachnick & Fidell, 2014).

All further assumptions of correlation and regression analysis were met. There were no tolerance statistics greater than .2, no issues with multicollinearity, and all inflation factors were below 10. All Dublin-Watson serial correlations were within the criteria of 2 (Field, 2013).

2.3.2 Descriptive Statistics

The descriptive statistics for demographics and measures are displayed in Table 5. Mean scores of trait anxiety ($M = 33.87$, $SD = 8.00$) were similar to levels observed in an asthmatic population (Trzanska et al., 2013), in an experimental study using ANT (Garner et al., 2011), and in a study using MCT (Boudrea et al., 2015); SD deviations varied in the dispersions.

Table 5
Descriptive Statistics for Demographics and Measures

Variable	Baseline *M* (*SD*)	Bronchoconstriction *M* (*SD*)	Bronchodilation *M* (*SD*)	Paired t–test between conditions
Sex	M = 38.2% F= 61.8%	-	-	

Age in years	39.4 (14.66)	-	-	
AE visit	0.03 (.171)	-	-	
GP visit	0.53 (1.35)	-	-	
Exacerbation	0.24 (0.606)	-	-	
AQLQ	6.03 (0.66)	-	-	
Activity	6.29 (0.60)	-	-	
Symptoms	5.90 (0.75)	-	-	
Emotion	6.19 (0.69)	-	-	
Environment	5.77 (1.0)	-	-	
ACQ	0.93 (.57)	-	-	
ACS	2.43 (0.26)	-	-	
Focus	2.42 (0.60)	-	-	
Shift	2.65 (0.53)	-	-	
Trait anxiety	33.87 (8.01)	-	-	
State anxiety	28.94 (7.02)	36.65 (9.41)	28.65 (6.70)	$t(30) = 4.39$, $p < .001$
Borg	0.46 (0.70)	2.37 (1.02)	0.113 (0.21)	$t(30) = 12.94$, $p < .001$
VAS breathlessness	18.36 (15.03)	73.63 (31.48)	16.39 (13.81)	$t(29) = 9.88$, $p<.001$
ANT				
Alerting	-	11.31 (23.72)	31.62 (27.50)	$t(25) = -3.99$, $p <.001$
Orienting	-	15.01 (31.02)	53.21 (15.55)	$t(25) = -.128$, $p =.899$
Executive	-	120.24 (83.63)	82.22 (31.15)	$t(25) = .107$, $p =.916$

Abbreviations: ACQ = Asthma Control Questionnaire, ACS = Attentional Control Scale, AE = Accident and Emergency, ANT = Attention Network Task, AQLQ = Asthma Quality of Life, GP = General Practise, STAI = State and Trait Anxiety Scale.

Breathlessness as measured by VAS was higher during bronchoconstriction (*M* = 73.63, *SD* = 31.48) compared to bronchodilation (*M* = 16.39, *SD* = 13.81), which is consistent with other experimental studies (Boudrea et al., 2015; De Peuter et al., 2006; Ritz et al., 2014). Borg measured the perceived feeling of bronchoconstriction and the increased perceived bronchoconstriction during the bronchoconstriction condition (M = 2.37, SD = 1.02) versus during bronchodilation (*M* = 0.113, *SD* = 0.21). AQLQ Total (*M* = 6.03, *SD* = 0.66) and the subscale of the Activity Limitation (M = 6.29, SD = 0.60) was higher than reported in previous studies, whilst Symptomology (*M* = 5.90, *SD* = 0.75), Emotional Functioning (*M* = 6.19. *SD* = .69), and Environmental Stimuli (*M* = 5.77, *SD*= 1.0) were similar (Deshmukh et al., 2008; Wang et al., 2010). The control (*M* = .93, *SD* = .57) reported in this study had better results than a previous reported study (Boudrea et al., 2015)

A paired t-test was conducted to see if there was a change in outcome measures while in a state of bronchoconstriction in comparison to bronchodilation. The analysis revealed significant differences between the conditions: State Anxiety was higher in bronchoconstriction (*M* = 36.65, *SD* = 9.41) than bronchodilation (*M* = 28.65, *SD* = 6.70); Alerting (ANT) was quicker in response in bronchoconstriction (*M* = 11.31, *SD* = 23.72) than during bronchodilation (*M* = 31.62, *SD* = 27.50); subjective perception of bronchoconstriction (BORG) was higher in bronchoconstriction(*M* = 2.37, *SD* = 1.02) than bronchodilation (*M* = .11, *SD* = .21), and breathlessness (VAS) was higher in bronchoconstriction (*M* = 73.63, *SD* = 31.48) than bronchodilation (*M* = 16.39, *SD*= 13.81).

2.3.3 Demographic Variables

The age of the participants (*M* = 39.4, *SD* = 14.66) is similar to various studies (Ciprandi et al., 2015, De Pueter et al., 2007; Yang et al., 2016). This study included more females than males, 61.8% vs 38.2%; this is not unexpected because a large number of

studies published in this area have included a higher percentage of females than males (66.97%, Feldman et al., 2009; 65.1%, Pilipenko et al., 2016; 62.5%, Wang et al, 2010).

2.3.4 Hypothesis One: Does perceived breathlessness change when anxious during bronchoconstriction and bronchodilation?

There were positive associations between state anxiety and perceptions of breathlessness at baseline (r = .522, p = .004), during bronchoconstriction (r = .482, p = .008), and following administration of bronchodilator medication (r = .479, p = .009).

2.3.5 Hypothesis Two: does anxiety or lung function predict perceived breathlessness?

Hierarchical multiple regression analysis was conducted using block-wise entry, with age and sex entered in block 1, anxiety in block 2, and lung function as assessed by spirometry entered in block 3.

Anxiety significantly predicted the perception of breathlessness (R^2 = .527, F[3, 29] = 3.34, p = .035, 95% CI .08 to 2.86) during bronchoconstriction. State anxiety during bronchoconstriction accounted for 52.7% of the variance. As expected, lung function was not a predictor of perception of breathlessness (R^2 = .540, F[5, 29] = 4.87, p = .119, 95% CI −2.29 to .85).

2.3.6 Hypothesis Three: does anxiety and perceived breathlessness predict quality of life, control, and healthcare utilisation?

2.3.6.1 Trait anxiety

Baseline trait anxiety was positively correlated with Asthma Control (ACQ), r(30) = .587, p = .001, and Attentional Focus (ACS), r(30) = .532, p = .002. As symptoms of anxiety increased, there was an increase in attentional focus and increasingly poor control of asthma.

Trait anxiety also significantly correlated negatively with AQLQ Total, $r(30) = -.518$, $p = .003$); the Emotional subscale of AQLQ, $r(30) = -.586$, $p = .001$; Symptomology, $r(30) = -.460$, $p = .011$; and Activity Limitation, $r(30) = -.517$, $p = .003$. Increased anxiety was associated with decreases in asthma quality of life. No significant correlations were detected between anxiety and the AQLQ Environmental subscale, $r(30) = -.310$, $p = .096$, or anxiety.

*Regression analysis***.** Given the significant correlations between Anxiety and AQLQ (and Control), a hierarchical multiple regression was computed using block wise entry, an alternative to stepwise regression chosen due to the issues associated with the analysis.

After accounting for sex and age, asthma related quality of life was significantly predicted by trait anxiety ($R^2 = .278$, $F[3, 27] = 3.34$, $p = .035$, 95% CI −.07 to −.03), 27.8% of the variance was accounted for by trait anxiety.

Hierarchical multiple regression analysis was utilised to identify predictors of asthma control, controlling for sex and age. Trait anxiety significantly predicted control ($R^2 = .360$, $F[3, 29] = 4.87$, $p = .008$, 95% CI .03 to .03), with 36% of variance accounted for by trait anxiety.

2.3.6.2 Health care utilisation

There were no correlations between trait anxiety and self-reported use of healthcare utilisation in the last 12 months for AE ($r = .003$, $p = .987$) or GP ($r = .101$, $p = .594$). There was no correlation between trait anxiety and exacerbation in the last 12 months ($r = .192$, $p = .309$).

Similarly, perceptions of breathlessness during bronchoconstriction ($r = -.352$, $p = .057$) and bronchodilation ($r = -.048$, $p = .803$) were not associated with the use of AE. Corresponding to GP and exacerbation, there was no association with breathlessness. However, there was an association between exacerbation and GP use in the last 12 months ($r = .733$, $p = .000$)

2.3.6.3 Breathlessness

Breathlessness (VAS) was measured at three time points: baseline, during bronchoconstriction, and during bronchodilation. There were no significant associations between perceived breathlessness and any other subscale or total of asthma quality of life (see Table 6 for further details), excluding the emotional subscale that showed a negative association ($r = -406$, $p = 029$). There were no significant associations between asthma control and perceived breathlessness at bronchoconstriction ($r = -.048$, $p = .804$) or at bronchodilation ($r = -.212$, $p = .270$).

Table 6
Pearson's correlations between breathlessness and AQLQ

	Bronchoconstriction	Bronchodilation	Differences
AQLQ total	−.163	−.269	.046
Activity	−.302	−.287	.191
Symptomology	−.087	−.236	−.022
Emotional	−.813	−.406*	.000
Environment	−.300	−.029	.319

*Significant at .05 Bootstrapping utilised to account for non-parametric analysis

2.3.7 Hypothesis Four: does asthma perception or anxiety correlate with reduced attention control, as measured by the computerized Attention Network Test?

2.3.7.1 ANT

Trait anxiety and perceptions of breathlessness (as measured by VAS) did not correlate with attentional alerting, orienting, or executive functioning during any of the experimental conditions. Table 7 displays the results from correlation analyses between the ANT and breathlessness and anxiety.

Table 7
Correlations during bronchoconstriction, bronchodilation and differences

	Bronchoconstriction	Bronchodilation	Difference

	Trait Anxiety	Breath-lessness	Trait Anxiety	Breath-lessness	Trait Anxiety	Breath-lessness
Alerting	.202	−.055	−.029	−.042	−.201	−.052
Orienting	.124	−.226	−.300	.084	−.358	−.335
Executive	−.309	.168	−.293	.238	−.064	−.069

Measuring the difference triggered by MCT and Post. Bootstrapping utilised to account for non-parametric analysis

2.3.7.3 ACS

Attentional Control did not significantly correlate with anxiety, $r(30) = .134$, $p = .179$. A negative correlation was observed between trait anxiety and the ACS Shift scale, $r(30) = -.571$, $p = .001$. This means as anxiety increased, the ability to disengage from a distraction to a new task decreased. A positive correlation was reported between ACS Focus, $r(30) = -.532$, $p = .002$. As anxiety increased, the ability to maintain engagement when distracted also increased. A negative relationship was detected between breathlessness and ACS shift during bronchoconstriction ($r = -.395$, $p = .031$). No further relationships were detected between self-reported measures of ACS and breathlessness during any of the conditions.

2.4 Discussion

This study set out to explore the relationship between anxiety and asthma, the effect of anxiety on breathlessness, and the subsequent effect of perceived breathlessness on measures of quality of life and control of asthma. Furthermore, the study explored attentional bias in both perceptions of breathlessness and anxiety using a computer task and self-report measures to inform subsequent targeting of mechanisms in psychological interventions. This experimental study induced bronchoconstriction in a laboratory setting to mimic an ‘asthma attack’ and gain an understanding of the allocation of attentional resources in different conditions.

The outcome measures and an attentional network of alerting showed significant differences when compared during bronchoconstriction and bronchodilation. This indicates

that experimental conditions affected several measures of anxiety, attentional resources for alerting, perceived breathlessness as per the hypothesis, and self-reports of bronchoconstriction. Subsequently, the analysis explored associations between the changes to identify any relationships with anxiety or breathlessness.

The first and second hypotheses were explored to reiterate previous findings of an association between perceived breathlessness and anxiety (Boudreau et al., 2015; Ciprandi et al., 2016; Lavietes, 2015; Nowobilski et al., 2009). The findings also highlighted that perceived breathlessness was better predicted by anxiety than by the physiological marker of lung function, and it accounted for half of the variance.

There was no significant association between trait anxiety and health care use in this study, consistent with Kullowatz et al. (2006). However, numerous studies have reported a link. Furthermore, studies have indicated that perception of symptoms is a predictor of healthcare use (Pilipenko et al., 2016; Schneider et al., 2007). It appears the findings in this study do not support previous research because there was no significant association with the perceived symptom of breathlessness and healthcare use. This discrepancy could be a reflection of the retrospective element, which is a source of error and bias in reporting. In addition, it could be that where there is increased awareness of symptoms, this motivated this cohort of asthmatics to self-medicate and therefore not access healthcare services. As expected, there was an association between exacerbations experienced in the last 12 months and GP use.

In respect to trait anxiety, the analysis revealed a significant positive association between control and asthma quality of life; because ACQ is measured with higher scores indicating worse control, a positive correlation signifies that the higher the symptoms of anxiety the worse the control. This is consistent with previous studies that reported negative correlations between anxiety and control (Avallone et al., 2012; Ciprandi et al., 2015; Viera

et al., 2011). The ACQ has questions that measure symptoms experienced in the morning or in the last week and these questions have subjective influences in interpretation. It is plausible theoretically that the agent of fear and hypervigilance concomitant with anxiety may influence a narrative of uncontrolled illness from a more heightened awareness of internal functioning, but this is contradictory to the findings by Furgal et al. (2011) and Di Marco et al. (2010), reporting an increased level of control with increased symptoms of anxiety. Alternatively, this could be explained by anxiety encouraging intake of medication and better control of their illness due to internal sensitivity.

Consistent with this theory, there should be an indication that internal judgements, such as breathlessness, would also propel action to gain better control. The findings are not consistent with this theory because the analysis revealed no significant association between perceived breathlessness and control, which conceivably indicates that perception of breathlessness does not affect control. The findings are inconsistent with Janssens et al. (2012), who reported higher symptoms during bronchoconstriction predicted control. Ciprandi et al. (2016) also reported that increased breathlessness was associated with decreased asthma control. Additionally, asthma quality of life was not associated with perceived breathlessness.

Methods of assessing perceived breathlessness differed across the studies and may account for the inconsistent findings. Janssens et al. (2012) explored perceptions of symptoms and not perceptions of breathlessness by itself. Additionally, they had adopted an ambiguous bronchoconstriction procedure with participants who had previously not undergone bronchoconstriction in a laboratory setting. Janssens et al. (2012) postulated that the ambiguity predicted outcome measures such as quality of life and control. The current study did not replicate some of the conditions, such as ambiguity, to measure perceived breathlessness, and thus the design of the current study may have affected the findings.

Alternatively, it could be that perceived breathlessness, a cornerstone of asthma management, does not affect quality of life and control.

Cognitive mechanisms were assessed during bronchodilation and bronchoconstriction to explore the association with anxiety and perceived breathlessness. Alerting, Orienting, and Executive Control networks were not associated with anxiety or perceptions of breathlessness. This is not entirely unexpected because two of the three attentional networks revealed no differences across the conditions (bronchoconstriction vs. bronchodilation); conceivably, the MCT challenge does not alter the allocation of attentional resources. There have been several studies that have shown a mixed effect of attentional network as measured by the ANT. Previous studies have shown no effect on alerting and orienting, but did find deficits in executive control when anxious, dependent on the measure of anxiety being a trait or a state (Pacheco-Unguetti, Acosta, Callejas, & Lupiánez, 2010), while others have shown increased alerting performance (Dennis et al., 2008). The means of all of the networks indicate a move in the correct direction of swifter response times for alerting and orienting and deficits in executive control highlighted by slower processing in the MCT challenge. In relationship to the significant differences in the alerting attentional network, the response times are swifter in the bronchoconstriction condition than the bronchodilation, plausibly indicating the bottom-up processing indicated by the ACT (Eysenck et al., 2007). Bottom-up processes posit that attention is driven by a stimulus, in this case the reduced lung function by 80%, increasing the need to become alert to stress (Pacheco-Unguetti et al., 2010).

Correlational analysis did not detect a significant difference, but plausibly the small sample size that was reduced considerably during the coding of the data may have lost statistical power. The ANT programme used for this study did not have any emotional-threat stimuli, which have been used in previous research to highlight attentional responses. Alternatively, attentional bias may not exist in the predictors measured in this study, which

has been shown to not exist in other chronic health conditions, such as chronic fatigue syndrome (Martin & Alexeeva, 2009).

On the other hand, the self-report attentional measure (ACS) contained greater data which increased the possibility of capturing an effect, unlike ANT were one third of the data was corrupted. Trait anxiety in asthmatics was found to be associated with a poorer ability to shift attention away from distractions, a consistent finding with other studies on the trait (Wilson, Vine, & Wood, 2009). This association may better account for poorer control in this current study, because this group of participants were unable to shift their attention due to their heightening anxiety, and consequently were unable to attend to better control of their symptoms. This was further supported by the association of perceived breathlessness and reduced ability to shift attention away from distractions (reduced lung function) during bronchoconstriction.

Caution is advised in interpreting the findings due to some limitations of the study. First, this study has a small sample size and therefore limited generalizability. However, the study did not include severe asthmatics in the sample due to the pre-requisite conditions of the MCT and therefore the findings are applicable to primary care management of asthma. Also, spirometry enabled the use of confirmed diagnosis of asthmatics as participants rather than relying on self-reported asthma diagnoses.

Second, the order of conditions was not varied; bronchoconstriction and bronchodilation were implemented in the same order and therefore the results might have been affected by order effects. This order was used because participants had to withdraw from medications that would have affected their lung function and therefore they were not in optimal conditions for bronchodilation to measure the effect the condition had on measures and attention tasks.

Third, participants' previous experience of MCT was not recorded. A previous memory of an MCT procedure reduces the ambiguity of the situation, consequently hindering the process of capturing a more accurate representation of perceived breathlessness (De Pueter et al., 2007; Janssens et al., 2012).

Fourth, the study used a VAS to capture perceived breathlessness, although previous research has used the Asthma Symptom Checklist (ASC), a reliable and valid questionnaire, which includes a breathlessness subscale (Ritz, Bobb, Edwards, & Steptoe, 2001).

Finally, our tentative findings indicate the role of focus and shifting in asthma and anxiety. Although the ANT did not detect any association, this could due to the reduced sample size at this point or perhaps more emotional attention to threat-related measures of attention, such as dot probes, would be better suited to capturing attentional bias and should be considered for future directions of research. Mogg and Bradley (1995) measured attentional bias in a branch of anxiety, Generalised Anxiety Disorder (GAD), with one of the primary measuring tools being the dot-probe. The dot-probe provides present threatening stimuli, unlike the current ANT, and connects this with the existing threat component in anxiety. Studies have reported individuals with anxiety orient towards threatening stimulus compared to neutral stimulus (Mogg & Bradley, 1998). Furthermore, they show a shift of awareness towards threatening stimuli (Macleod et al., 1986).

2.4.1 Conclusion

This study has highlighted that changes in breathlessness are predicted by anxiety and that anxiety significantly predicts quality of life and control of asthma. The important role of anxiety on subjective perception of breathlessness and its effects on quality of life and the ability to control disease suggests psychological treatments are needed to improve the quality of asthma care.

The tentative results indicate the occurrence of shifting attentional bias in asthmatics experiencing increased breathlessness and subsequent anxiety. Given the lack of association between anxiety/breathlessness and ANT, further research is needed to explore attentional bias using different methods, such as the dot probe, to better explain the underlying mechanisms and to improve asthma care.

Appendix A – Early Models Conceptualising Anxiety

Anxiety Models

Learning theories have proposed that the associative learning between fear and the response mechanisms is learned through experience. An asthma attack in the absence of allergens is conceivably a result of classical conditioning (Purcell & Weiss, 1970). Classical conditioning posits that a neutral stimulus becomes associated with an aversive eliciting stimulus. Once an association has been made it will elicit a reflexive response in the presence of neutral stimulus. In the experiment devised by Ivan Pavlov, a young child was used to demonstrate learning of fear. An animal which was originally a neutral non-provoking stimulus was paired to loud sounds (aversive experience). Consequently, the animal becomes conditioned to be aversive for the child. Subsequently, the child became distressed upon seeing the animal or attempted to avoid it. However, the fear was short lived and lacked conceptualisation of longer-term anxiety. Arguably, in time the aversive eliciting conditioned stimulus prime generalisation of trepidation accompanying neurological processes (Dutke & Stober, 2001). Furthermore, classical conditioning has also been shown to evoke positive feelings using the same process, though using a favourable stimulus instead.

Classical conditioning emphasises the fear conditioned to a physical object, emphasising that acquisition of fear is a phobic reaction. However, several studies have refuted that aversive or traumatic incidents are implicated in the acquisition of anxiety (Edelman, 1992). The findings are perhaps more in line with the presentation of anxiety in physical health settings, where trauma or physical aversive objects are not coupled. The literature has highlighted induced bronchoconstriction in asthmatics in the absence of physical agents, which has been attributed to the perception of environmental agents that have the capability to elicit an exacerbation (Isenberg, Lehrer, & Hochron, 1992). Research has reported the higher perception of asthma environmental agents to be associated with

lower quality of life (Peterson, Gaeta, Birkhahn, Fernández, & Mancuso, 2012), physicians' ratings of asthma severity (Göksel et al., 2009), greater use of medication and a greater number of relapses (Peterson et al., 2012). The agent of fear can be attributed to perception, with a focus on perceived disaster. This can plausibly be accounted for by internal discernment with physical disaster (wheezing, pain in abdomen) or mental disorder or social catastrophe (Beck, Emery & Greenburg, 1985).

Appendix B - Quality Assessment

	Questions												
	Inc/Excl	Duration	Diagnosis	Recruit	Power	Stats	Environ	State-A	Trait-A	Depress	Control	QOL	Lung
Avallone et al. (2012)	Y	N	N	Y	N	N	Y	N	Y	N	Y	Y	N
Boudreau et al, (2015)	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y
Ciprandi et al. (2015)	Y	N	N	Y	N	N	N	N	Y	Y	Y	N	Y
Ciprandi et al. (2016)	Y	N	N	Y	N	Y	N	N	Y	Y	Y	N	Y
De Peuter et al, (2007)	Y	N	N	Y	N	Y	Y	Y	Y	N	N	N	Y
De Peuter et al., (2008)	N	N	N	N	N	Y	N	Y	N	N	N	N	Y
Deshmukh et al. (2008)	Y	N	N	Y	Y	Y	N	N	Y	Y	N	Y	N
Di Marco et al, (2009)	Y	Y	N	N	Y	Y	N	N	Y	Y	Y	N	Y
Feldman et al. (2009)	Y	N	N	Y	N	Y	Y	N	Y	N	N	Y	Y
Furgal et al. (2011)	N	Y	N	N	N	N	N	N	Y	Y	N	N	Y
Kullowatz, et al. (2007)	N	Y	Y	N	N	Y	N	N	Y	Y	N	Y	N
Lavietes (2015)	Y	N	N	N	N	Y	N	Y	Y	N	N	N	Y
Mosaku et al, 2011	Y	Y	N	Y	N	Y	N	N	Y	Y	N	Y	Y
Nowobilski et al, (2009)	N	Y	N	N	N	Y	N	Y	Y	Y	N	N	Y

Oga et al. (2007)	Y	N	N	Y	N	Y	N	N	Y	Y	N	Y	Y
Panek et al, (2015)	Y	Y	N	N	N	Y	N	Y	Y	Y	Y	N	Y
Pilipenko et al. (2016)	Y	N	N	Y	N	Y	N	N	Y	Y	Y	N	N
Ritz et al. (2014)	Y	N	N	Y	N	Y	Y	N	Y	Y	N	N	Y
Schneider et al, (2008)	Y	N	N	Y	N	Y	N	N	N	Y	N	Y	Y
Smith, et al. (2009)	Y	N	N	Y	N	Y	N	N	Y	Y	Y	N	Y
Smith et al, (2005)	N	N	Y	Y	N	Y	N	N	Y	Y	Y	Y	N
Trzcinska et al. (2013)	N	N	Y	Y	N	Y	N	Y	Y	Y	Y	N	N
Vieira et al. (2011)	Y	N	N	Y	N	Y	Y	N	Y	Y	Y	Y	Y
Wang et al, 2010	Y	Y	N	Y	Y	Y	N	N	Y	Y	Y	Y	Y
Yang et al. (2016)	Y	N	Y	N	N	Y	N	Y	N	Y	Y	N	N
Zhu et al, (2016)	Y	N	N	Y	N	Y	N	N	Y	Y	Y	Y	Y

**Asthma related quality of life is a metric for quantifying subjective perception of health status, functional status, social and/or emotional functioning in asthma sufferers (Wilson et al, 2012)*

Inc/Excl: Were inclusion /exclusion criteria specified?

Duration: Was information on duration of asthma diagnosis provided?

Diagnosis: Was the type of asthma diagnosis specified?

Recruit: Was the recruitment process clearly specified and defined?

Power : Was sample size justification or a power calculation provided?

Stats: Were statistical analyses appropriate?

Environ : Was the testing environment the same across all study participants?

State-A: Were levels of state anxiety assessed and data reported?

Trait-A: Were levels of trait anxiety assessed and data reported?

Depress: Were levels of depression assessed and data reported?

Control: Were levels of asthma control assessed and data reported?

QOL: Was asthma related quality of life assessed and data reported?*

Lung: Were measures of lung function (e.g. spirometry, peak flow) assessed and reported?

Appendix C – Recruitment Poster

Patient Advert, V2, 16/12/2015

Southampton NHS
University Hospitals NHS Trust

Asthma Research

Respiratory Biomedical Research Unit (RBRU)

Volunteers are needed to help us study the thought process of people with asthma.

If you have asthma, would you be willing to help? It would involve one session (lasting 2 hours) doing a breathing challenge while also completing some questionnaires and computer tasks.

Reimbursement would be provided for your time and travel expenses.

For more information, please contact the research team: rpni@soton.ac.uk.

Asthma Study Research Team:
rpni@soton.ac.uk
02380 591 950

Appendix D – Participant Information Sheet

Ethics submission number: **15/LO/1898**
v4: 11/1/2016

Southampton NHS
University Hospitals NHS Trust

Participant Information Sheet

Investigating thought processes in asthma

Name of Principal Investigator: Dr Ben Ainsworth
Chief Investigator: Professor Mike Thomas

Sponsor: University Hospital Southampton NHS Foundation Trust

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it would involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of this study?

This study aims to investigate the ways that thinking and feeling are affected by asthma, using some simple computer tasks and questionnaires during a brief period of mild induced asthma. We plan to ask people with asthma to take part in a 'methacholine challenge test', which temporarily induces mild asthma, and ask them to do these tasks in order to help us understand the ways in which thought processes are affected when asthma symptoms happen.

Methacholine is a drug which causes muscle contraction (narrowing) in the air tubes, which is what happens when asthma gets worse. Methacholine challenge testing is a commonly used and safe investigation used by doctors worldwide in the diagnosis and assessment of asthma. It a standard and safe test that is also used in many research studies of asthma. Under safe and controlled conditions, very low concentrations are inhaled and slowly increased until the airways start to tighten up a bit.

People who take part in the study will be asked complete some short and simple computer tasks and questionnaires before and after the methacholine challenge. These computer tasks and questionnaires will be used to understand participants' thought processes, and how they are affected by asthma. We think that as asthma gets worse, this can affect clear thinking and result in anxious feelings that make the asthma symptoms feel even worse. By understanding what happens to people during asthma attacks better, we hope that we can go on in future work to find ways to help people improve this anxiousness and lack of clear thinking and so cope better with asthma.

Why have I been chosen?

You have been chosen as you have asthma. You may have responded to an advertisement, your consultant may have felt that you would fit the study criteria, or you may be on our departmental volunteer database. You would be one of 40 participants.

Initially people who take part in the study will be asked if you would like to participate in this study. If you would like to, you will be asked to sign the consent form attached.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are

still free to withdraw at any time and without giving a reason. This would not affect the standard of care you receive.

What would happen to me if I take part?

You would need to attend ONE session at the hospital. If you agree to participate and are eligible to enroll into this study, your participation will be for a total duration of approximately 2 hours, in which you will complete the methacholine challenge, some questionnaires and some short computer tasks.

More details about the Methacholine Challenge

You will be asked, prior to attending for this session, not to use your rescue inhaler (e.g. Ventolin (Salbutamol) or Bricanyl) for 6 hours. If withholding your medication is not possible and you feel it necessary to use your inhalers, for example because of an asthma attack, please inform the research team that this has happened. Any anti-histamines, such as Clarityn or Piriteze, that you usually take should be stopped at least 4 days prior to this visit.

- At the visit a researcher will ask you some questions about your medical history and help you answer questions on some questionnaires.
- You will be asked to perform some simple breathing tests – these involve blowing into a tube (a spirometer, which you have probably done before) to measure your lung capacity and whether the tubes are narrowed.
- You will then be asked to inhale a drug called Methacholine which lets us assess how reactive to 'twitch' the muscles in your airways are. We start with a very low inhaled amount, and measure whether your lung tubes tighten at all by repeating the blowing test (spirometry). If they don't, or do so very little, a slightly higher dose inhalation will be given and the spirometry will be repeated. This will continue for up to 7 inhalations, stopping if you start to feel bad or when the blowing test has reduced to 4/5 of the original level. Inhaling this agent may make you wheeze or cough a bit. At the end of the test we will ask you to do the computer tasks again, and then we will give you some salbutamol (reliever inhaler medication) to reverse the effects of methacholine.
- You will be reimbursed for the time you donate to the study, up to £25, and any travel expenses up to a maximum of £25 (a total of up to £50). Were you to withdraw from the study at any point, you will be reimbursed on a pro rata basis for the time that you have already donated to the study.

What will happen to the information I have provided during this study?

Your personal details will be kept on a central database that will be accessible ONLY by the chief investigator of the study (Professor Mike Thomas) and the principal investigator (Dr Ben Ainsworth).

What are the computer tasks I will be asked to complete.

During the experiment you will be asked to complete two computer tasks; the visual probe task and the attention network test. Both of these tasks have been used extensively in psychology experiments and people generally find them simple and not stressful to do. Each test takes 5-8 minutes. In both tasks you will be asked to identify the directions of arrows appearing in different places, as quickly and accurately as possible. You will be given an opportunity to practice and ask

Appendix E - Consent

Southampton NHS
University Hospitals NHS Trust

CONSENT FORM

Name of researcher:

Subject identification number for this trial:

PLEASE **INITIAL** THE BOXES IF YOU AGREE WITH EACH SECTION:

1. I confirm that I have read the information sheet version 1 dated 2 September 2015 for the above study and have been given a copy to keep. I have been able to ask questions about the study and I understand why the research is being done and any risks involved. ☐
2. I agree to take part in the above study ☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected. ☐
4. I give permission for someone from the research team to look at my medical records to get information of relevance to this study. I understand that the information will be kept confidential. ☐
5. I understand that my GP will be informed of my participation in this study. ☐
6. I understand that my Doctor and I may be informed of any of the results of tests done as part of the research that are important for my health. However, I also understand that the research may not directly benefit my health. ☐
7. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from research regulatory authorities or from University of Southampton NHS Foundation Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
8. I understand that I will not benefit financially if this research leads to the development of a new treatment or test. ☐
9. I know how to contact the research team if I need to. ☐

Name of Patient	Date	Signature
Name of person taking consent (researcher)	Date	Signature

Appendix F – State-Trait Anxiety Inventory (STAI)

STAI

INSTRUCTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and circle the appropriate number to the right of the statement to indicate how you **generally** feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

		Not at all	Somewhat	Moderately so	Very much so
1)	I feel pleasant.....	1	2	3	4
2)	I feel nervous & restless.....	1	2	3	4
3)	I feel satisfied with myself.....	1	2	3	4
4)	I wish I could be as happy as others seem to be.....	1	2	3	4
5)	I feel like a failure	1	2	3	4
6)	I feel rested.....	1	2	3	4
7)	I am 'calm, cool and collected'.....	1	2	3	4
8)	I feel that difficulties are piling up so that I cannot overcome them.....	1	2	3	4
9)	I worry too much over something that doesn't really matter.....	1	2	3	4
10)	I am happy.....	1	2	3	4
11)	I have disturbing thoughts.....	1	2	3	4
12)	I lack self-confidence.....	1	2	3	4
13)	I feel secure.....	1	2	3	4
14)	I make decisions easily.....	1	2	3	4
15)	I feel inadequate.....	1	2	3	4
16)	I am content.....	1	2	3	4
17)	Some unimportant thought runs through my mind and bothers me.....	1	2	3	4
18)	I take disappointments so keenly that I can't put them out of my mind.....	1	2	3	4
19)	I am a steady person.....	1	2	3	4
20)	I get in a state of tension or turmoil as I think over my recent concerns and interests.....	1	2	3	4

SSAI

Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. Palo Alto CA: Consulting Psychologists' Press, 1983

INSTRUCTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and circle the appropriate number to the right of the statement to indicate how you feel **RIGHT NOW**. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

		Not at all	Somewhat	Moderately so	Very much so
1)	I feel calm	1	2	3	4
2)	I feel secure	1	2	3	4
3)	I am tense	1	2	3	4
4)	I feel strained	1	2	3	4
5)	I feel at ease	1	2	3	4
6)	I feel upset	1	2	3	4
7)	I am presently worrying over possible misfortunes	1	2	3	4
8)	I feel satisfied	1	2	3	4
9)	I feel frightened	1	2	3	4
10)	I feel comfortable	1	2	3	4
11)	I feel self-confident	1	2	3	4
12)	I feel nervous	1	2	3	4
13)	I am jittery	1	2	3	4
14)	I feel indecisive	1	2	3	4
15)	I am relaxed	1	2	3	4
16)	I feel content	1	2	3	4
17)	I am worried	1	2	3	4
18)	I feel confused	1	2	3	4
19)	I feel steady	1	2	3	4
20)	I feel pleasant	1	2	3	4

Appendix G – Visual Analogue Scale (VAS).

VAS-2

Put a vertical line at an appropriate point on the line below to indicate **HOW YOU ARE FEELING RIGHT NOW** with regard to that word.

BREATHLESS

Not at all	A little	Moderately	Quite a lot	Extremely
.....				.....

Appendix H - The Standardized Asthma Quality of Life Questionnaire (AQLQ (S))

AQLQ (S)

Please answer the questions in the order they are presented. Please complete all questions by selecting the number that best describes how you have been during the last two weeks in these activities as a result of your asthma.

How limited have you been **during the last two weeks** in these activities **as a result of your asthma?**

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
1. **Strenuous activities** (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
2. **Moderate activities** (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
3. **Social activities** (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
4. **Work related activities** (tasks you have to do at work. If you are not employed, or self-employed, these should be task you have to do most days)	1	2	3	4	5	6	7
5. **Sleeping**	1	2	3	4	5	6	7

How much **discomfort or distress** have you felt **during the last 2 weeks**?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
6. How much discomfort or distress have you felt over the last two weeks as a result of **chest tightness?**	1	2	3	4	5	6	7

In general, **how much of the time during the last two weeks** did you:

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
7. Feel **concerned about having asthma?**	1	2	3	4	5	6	7
8. Feel **short of breath** as a result of your asthma?	1	2	3	4	5	6	7
9. Experience asthma symptoms as a **result of being exposed to cigarette smoke?**	1	2	3	4	5	6	7
10. Experience a **wheeze** in your chest?	1	2	3	4	5	6	7
11. Feel you had to **avoid a situation or environment because of cigarette smoke.**	1	2	3	4	5	6	7

How much **discomfort or distress** have you felt **during the last 2 weeks**?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
12. How much discomfort or distress have you felt over the last two weeks as a result of **coughing?**	1	2	3	4	5	6	7

In general, **how much of the time during the last two weeks** did you:

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
13. Feel **frustrated** as a result of your asthma?	1	2	3	4	5	6	7
14. Experience a feeling of **chest heaviness.**	1	2	3	4	5	6	7
15. Feel **concerned about the need to use medication** for your asthma.	1	2	3	4	5	6	7
16. Feel the need to **clear your throat?**	1	2	3	4	5	6	7
17. Experience asthma symptoms as a **result of being exposed to dust**	1	2	3	4	5	6	7
18. Experience **difficulty breathing as a result of your asthma**	1	2	3	4	5	6	7
19. Feel you had to **avoid a situation or environment because of dust.**	1	2	3	4	5	6	7
20. **Wake up in the morning with asthma symptoms**	1	2	3	4	5	6	7
21. Feel **afraid of not having your asthma medication available.**	1	2	3	4	5	6	7
22. Feel bothered by **heavy breathing.**	1	2	3	4	5	6	7
23. Experience asthma symptoms as a **result of the weather or air pollution outside?**	1	2	3	4	5	6	7
24. Were you **woken at night** by your asthma?	1	2	3	4	5	6	7
25. **Avoid or limit going outside because of the weather or air pollution?**	1	2	3	4	5	6	7
26. Experience asthma symptoms as a **result of being exposed to strong smells or perfume.**	1	2	3	4	5	6	7
27. Feel **afraid of getting out of breath.**	1	2	3	4	5	6	7
28. Feel you had to **avoid a situation or environment because of strong smells or perfume.**	1	2	3	4	5	6	7
29. Has your asthma **interfered with getting a good night's sleep?**	1	2	3	4	5	6	7
30. Have a feeling of **fighting for air?**	1	2	3	4	5	6	7

How limited have you been **during the last two weeks**:

	Severely Limited Most Not Done	Very Limited	Moderately Limited Several not done	Slightly Limited	Very Slightly Limited Very Few not done	Hardly Limited at all	Not Limited Have done all activities
31. Think of the **the overall range of activities** that you would have liked to have done during the last 2 weeks. How much has your range of activities been limited by your asthma?	1	2	3	4	5	6	7

How limited have you been **during the last two weeks**:

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
32. Overall, among **all the activities** that you have done during the last 2 weeks, how limited have you been by your asthma?	1	2	3	4	5	6	7

Appendix I - Asthma Control Questionnaire (ACQ).

ACQ

Please answer Questions 1–6.
Circle the number of the response that best describes how you have been during the past week.

1. On average, during the past week, how often were you woken by your asthma during the night?	0 Never 1 Hardly ever 2 A few times 3 Several times 4 Many times 5 A great many times 6 Unable to sleep because of asthma
2. On average, during the past week, how bad were your asthma symptoms when you woke up in the morning?	0 No symptoms 1 Very mild symptoms 2 Mild symptoms 3 Moderate symptoms 4 Quite severe symptoms 5 Severe symptoms 6 Very severe symptoms
3. In general, during the past week, how limited were you in your activities because of your asthma?	0 Not limited at all 1 Very slightly limited 2 Slightly limited 3 Moderately limited 4 Very limited 5 Extremely limited 6 Totally limited
4. In general, during the past week, how much shortness of breath did you experience because of your asthma?	0 None 1 A very little 2 A little 3 A moderate amount 4 Quite a lot 5 A great deal 6 A very great deal
5. In general, during the past week, how much of the time did you wheeze?	0 Not at all 1 Hardly any of the time 2 A little of the time 3 A moderate amount of the time 4 A lot of the time 5 Most of the time 6 All the time
6. On average, during the past week, how many puffs of short acting bronchodilator (e.g., Ventolin) have you used each day?	0 None 1 1–2 puffs most days 2 3–4 puffs most days 3 5–8 puffs most days 4 9–12 puffs most days 5 13–16 puffs most days 6 More than 16 puffs most days
7. FEV1 prebronchodilator: ..... FEV1 predicted..... FEV1% predicted..... (Record actual values on the dotted lines and score the FEV1% predicted)	0 > 95% predicted 1 95–90% 2 89–80% 3 79–70% 4 69–60% 5 59–50% 6 < 50% predicted

Appendix J – Borg Scale

BORG

Please indicate on the scale below how breathless you are feeling RIGHT NOW.

Scale	Severity
0	No Breathlessness At All
0.5	Very Very Slight (Just Noticeable)
1	Very Slight
2	Slight Breathlessness
3	Moderate
4	Some What Severe
5	Severe Breathlessness
6	
7	
8	Very Severe Breathlessness
9	
10	Very Very Severe (Almost Maximum)

Appendix K - The Attention Control Scale (ACS).

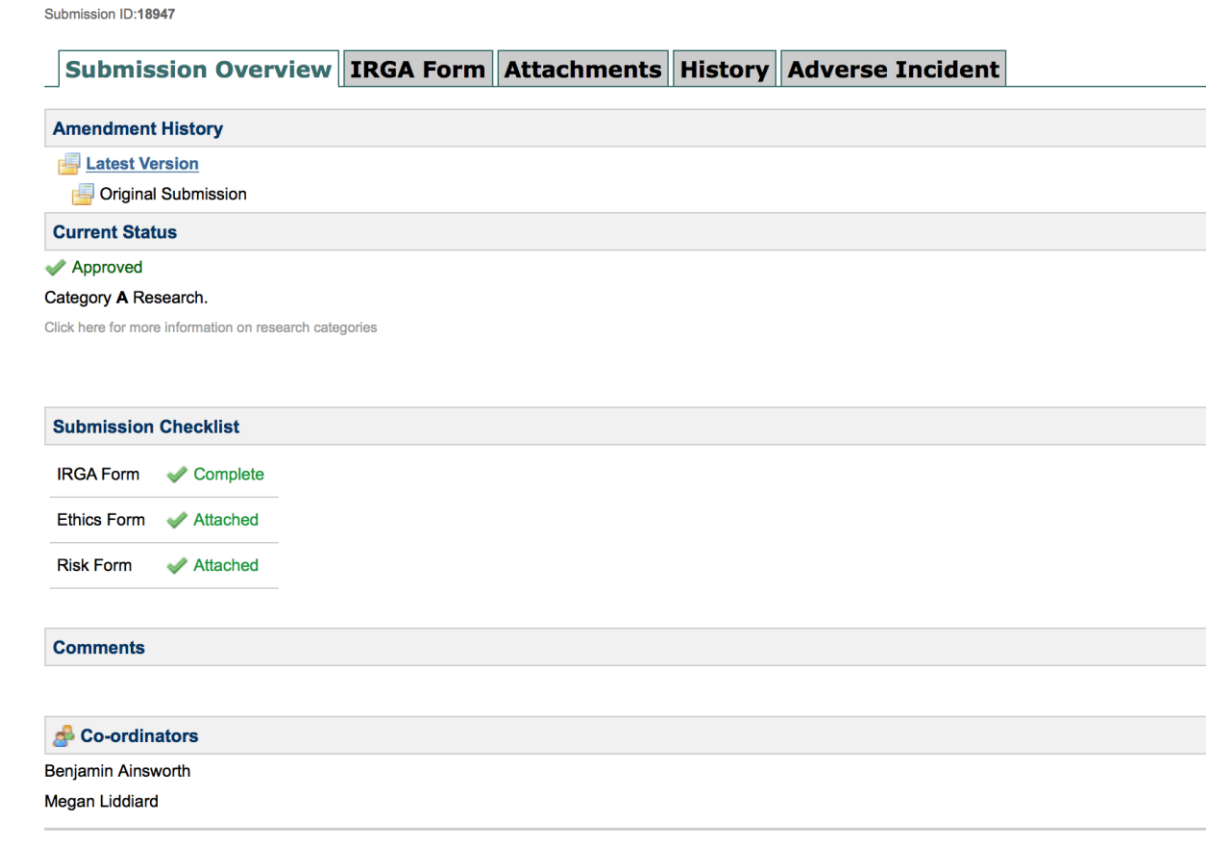
ACS

Please rate each of these items on a scale of 1 (almost never) to 4 (always).

1=almost never; 2=sometimes; 3=often; 4=always

1.	It's very hard for me to concentrate on a difficult task when there are noises around.	1	2	3	4
2.	When I need to concentrate and solve a problem, I have trouble focusing my attention.	1	2	3	4
3.	When I am working hard on something, I still get distracted by events around me.	1	2	3	4
4.	My concentration is good even if there is music in the room around me.	1	2	3	4
5.	When concentrating, I can focus my attention so that I become unaware of what's going on in the room around me.	1	2	3	4
6.	When I am reading or studying, I am easily distracted if there are people talking in the same room.	1	2	3	4
7.	When trying to focus my attention on something, I have difficulty blocking out distracting thoughts.	1	2	3	4
8.	I have a hard time concentrating when I am excited about something.	1	2	3	4
9.	When concentrating I ignore feelings of hunger or thirst.	1	2	3	4
10.	I can quickly switch from one task to another.	1	2	3	4
11.	It takes me a while to get really involved in a new task.	1	2	3	4
12.	It is difficult for me to coordinate my attention between the listening and writing required when taking notes during lectures.	1	2	3	4
13.	I can become interested in a new topic very quickly if I need to.	1	2	3	4
14.	It is easy for me to read or write while I'm also talking on the phone.	1	2	3	4
15.	I have trouble carrying on two conversations at once.	1	2	3	4
16.	I have a hard time coming up with new ideas quickly.	1	2	3	4
17.	After being interrupted or distracted, I can easily shift my attention back to what I was doing before.	1	2	3	4
18.	When a distracting thought comes to mind, it is easy for me to shift my attention away from it.	1	2	3	4
19.	It is easy for me to alternate between two different tasks	1	2	3	4
20.	It is hard for me to break from one way of thinking about something and look at it from another point of view.	1	2	3	4

Appendix L- University Ethics



Submission ID:18947

Submission Overview | IRGA Form | Attachments | History | Adverse Incident

Amendment History

Latest Version

Original Submission

Current Status

Approved

Category **A** Research.

Click here for more information on research categories

Submission Checklist

IRGA Form	Complete
Ethics Form	Attached
Risk Form	Attached

Comments

Co-ordinators

Benjamin Ainsworth

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Appendix M – NHS Ethics

NHS
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13 January 2016

Prof Mike Thomas
Professor of Primary Care
University of Southampton
Aldermoor Health Centre
Aldermoor Road
Southampton SO16 5ST

Dear Prof Thomas

Study title:	**Investigating maladaptive cognitive biases in patients with asthma using a bronchial hyperreactivity challenge.**
REC reference:	**15/LO/1898**
IRAS project ID:	**187616**

Thank you for your letter of 12 January 2016, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a Sub-Committee of the REC in correspondence. A list of the Sub-Committee members is attached.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Mr Raj Khullar, nrescommittee.london-cityroadandhampstead@nhs.net.

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.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

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