TITLE: Multidimensional Assessment of Severe Asthma: A Systematic Review and Meta-Analysis.

Authors' full names: Vanessa L Clark[1,2] Peter G Gibson[1,3,] Grayson Genn[1], Ian D Pavord[4] , Vanessa M McDonald[1,2,3]

Authors' affiliation(s):

[1]National Health and Medical Research Council Centre for Research Excellence in Severe Asthma and The Priority Research Centre for Healthy Lungs. The University of Newcastle, NSW, Australia

[2]School of Nursing and Midwifery, The University of Newcastle, NSW, Australia

[3]Department of Respiratory and Sleep Medicine, John Hunter Hospital, Hunter Medical Research Institute, NSW, Australia

[4] Respiratory Medicine Unit, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom

Corresponding author full contact details:

Name: Professor Vanessa McDonald
Address: Hunter Medical Research Institute.
Level 2 West Wing, HMRI Building, Lot 1 Kookaburra Circuit
Post code: 2305
City: Newcastle
Country: Australia
Email: Vanessa.McDonald@newcatle.edu.au
Twitter account name (optional): @SevereAsthmaCRE @nessmcd

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ABSTRACT: *(maximum 250 words; no sub-headings)*

The management of severe asthma is complex. Multidimensional assessment (MDA) of specific traits has been proposed as an effective strategy to manage severe asthma although, is supported by limited prospective studies.

We aim to systematically review the literature published on MDA in severe asthma, to identify the traits included in MDA and to determine the effect of MDA on asthma related outcomes.

We identified 26 studies and classified these based on study type (cohort/cross sectional studies; experimental/outcome studies; and severe asthma disease registries). Study type determined the comprehensiveness of the assessment. Assessed traits were classified into three domains (airways, comorbidities and risk factors). The airway domain had the largest number of traits assessed (M±SD, 4.2±1.7) compared to comorbidities (3.6±2.2) and risk factors (3.9±2.1). Bronchodilator reversibility and airflow limitation were assessed in 92% of studies, whereas airway inflammation was only assessed in 50%. Commonly assessed comorbidities were psychological dysfunction (73%), sinusitis (73%) and GORD (69%). Atopic and smoking status were the most commonly assessed risk factors (85 and 86%, respectively).

There were six outcome studies, of which five concluded that MDA is effective. Among these studies significantly more traits were assessed than treated.

Multidimensional Assessment studies have assessed a variety of different traits and have shown evidence of improved outcomes. This promising model of care requires more research to inform what traits should be assessed, what traits should be treated and what effect it has on patient outcomes.

Short title: *Multidimensional Assessment in Severe Asthma*

Keywords: Severe Asthma;
(five words selected from the list recommended by the US National Library of Medicine's Medical Subject Headings (MeSH)

Introduction

Severe asthma is a complex chronic disease which is underpinned by several phenotypes and impacted by various comorbidities and risk factors. The approach to management of severe asthma is complicated by the heterogeneous nature of the disease and the prevalence of associated comorbidities. To optimise management of severe asthma individuals also require a set of self-management skills and behaviours. Therefore asthma management needs careful and multidimensional assessment, which may involve airway pathobiology, comorbidities, risk factors and self-management skills (1). In recent years there have been several recommendations by guideline committees and key opinion leaders promoting, in some form or another, multidimensional assessment and targeted treatment for airway disease management (2-4). These approaches are based on a precision medicine model, which has been shown to be effective in the management of other complex chronic diseases (5). Precision medicine is an approach that targets treatment to an individual patient, on the basis of the individual's genetic, phenotypic, biomarker or psychosocial characteristics (5). Multidimensional assessment is a proposed method of determining those characteristics, so that treatment can be targeted accordingly. A precision medicine approach may be beneficial for severe asthma as it accounts for the variation in the common biological processes that underpin the disease, whilst considering the different disease processes, risk factors and comorbidities that impact severe asthma.

Multidimensional assessment or 'systematic assessment' for severe asthma was first proposed by Irwin et al. in 1993 (6). Since then, advances in the understanding of mechanisms and biological pathways, otherwise referred to as 'endotypes' (for example, the eosinophilic and neutrophil airway inflammatory endotypes), together with advanced assessment and management of severe asthma have allowed better treatment precision and the development of targeted biological treatments (7). Theoretical examples of how the multidimensional assessment and targeted treatment approach can be applied in a complex airway disease have been suggested (2, 8, 9) and in 2016 Agusti et al. (3) proposed a 'treatable traits of airway diseases' model. Each of these models proposes the assessment of several key domains that impact airway disease management. Gibson et al. (2) suggested that the key domains for targeted treatment should be airways, relevant comorbidities, self-management skills and risk factors. A pilot study of this approach in COPD led to significant improvements in health outcomes (10). More recently the authors collapsed the latter two categories to create the CARe (comorbidities, airways and risk factors) model of assessment (11). The "treatable traits" model suggests assessment along the domains of pulmonary traits, extra pulmonary traits and behavioural risk factors (3). These approaches allow for the

diagnosis of chronic airway disease to be confirmed and for the complexity of airway disease to be considered and managed accordingly.

The terms multidimensional assessment, systematic assessment and more recently, treatable traits are often used interchangeably. For the purpose of this review, we will use the term “multidimensional assessment” to mean the assessment of severe asthma across more than one domain, including airway, comorbidity and risk factor assessment.

Whilst there has been theoretical support for the multidimensional approach, little data exists to inform its effectiveness in assessment or management of severe asthma. In this systematic review we aim to examine the literature that has been published to date on multidimensional assessment, and where possible draw conclusions about its effectiveness and clinical applications. Specifically, we will examine: What traits, including comorbidities are being measured in severe asthma? The consensus of what is being measured among studies? What is the effect of multidimensional assessment? What are the most prominent comorbidities reported across all studies? As well as comparing the assessments in these studies to key recommendations for multidimensional assessment of severe asthma patients in the literature.

Methods

Study Design

We conducted a systematic review to assess the literature that has been published on the topic of multidimensional assessment in severe asthma up to May 2017. Additionally we conducted a meta-analysis of the studies that reported relevant comparable outcomes.

Eligibility criteria

Criteria for study inclusion were those that involved: (1) adult participants (≥ 18 years) with a diagnosis of severe, or difficult to treat asthma, (2) a multidimensional assessment of severe or difficult to treat asthma participants, (3) studies that included data from the multidimensional assessment (ie. review articles or recommendations were not included) and, (4) full text publications article in peer reviewed journals using English language.

Definitions

The European Respiratory Society/ American Thoracic Society (ATS/ERS) guidelines characterises severe asthma as requiring high dose inhaled corticosteroids (ICS) or the

need for systemic steroids for greater than 50% of the previous year (12). The World Health Organisation further classifies severe asthma into three categories (13); untreated severe asthma, where access to treatment might be limited, for example in developing nations; difficult-to-treat severe asthma, where the patient's asthma may be adversely affected by poor inhaler technique, non-adherence, exposure to triggers and/or related comorbidities, such as sinusitis; and treatment resistant severe asthma, where asthma remains uncontrolled, regardless of adequate self-management skills, high dose medication and treatment of related comorbidities (14). The focus of this systematic review will be on both difficult-to-treat severe asthma, and treatment resistant severe asthma.

Multidimensional assessment is defined as a coordinated series of investigations and assessments, designed to confirm diagnosis or highlight mechanisms of persisting symptoms (such as phenotyping); or identify comorbidities relevant to severe asthma; or identify risk factors. *The multidimensional assessment needed to consist of at least two of the following domains: airways and comorbidities, or airways and risk factors (2, 3, 15), in addition to the inclusion of at least two assessed traits within each domain."*

Search strategies

A computerised search of Cochrane, Medline, EMBASE, CINAHL and medline in process databases was conducted using key words related to severe asthma ("asthma" or "severe asthma" or "disease refractory asthma" or "treatment resistant asthma" or "difficult asthma" or "difficult to treat asthma" or "therapy-resistant asthma" or "steroid-dependent asthma" or "brittle asthma") and key words relating to multidimensional assessment ("systematic assessment" or "multidimensional assessment" or "treatable traits" or "comorbid" or "comorbidity assessment" or "global assessment" or "precision medicine" or "disease management"). An example of the search strategy can be found in the supplementary material.

Articles were limited to English language and human participants. An additional manual search of the reference lists of included studies was conducted. The abstracts were screened for relevance by two researchers (VC and GG), and then full text articles were obtained for the relevant articles. Study selection is outlined in Figure 1. Articles were also rated for quality by two raters (VC and GG) using the National Institutes of Health: National Heart, Lung and Blood Institute, Quality assessment tool for observational cohort and cross sectional studies. Each study was given a rating (good, fair or poor) based on a series of questions related to study methodology. When agreement could not be reached a third rater

(VMcD) made the final decision. The traits assessed in the included articles were compared to the traits suggested for assessment by four key recommendations that propose a multidimensional approach (2-4, 12). If the recommendation suggested that a particular trait be assessed and/or treated in severe asthma, they are denoted with a symbol.

Data Analysis

Data analysis were conducted using SPSS (version 24, Chicago, IL, USA) and Comprehensive Meta-analysis V3 (Biostat, Inc, USA). The variables of interest were extracted manually from the papers. In studies that reported data for a number of different categories of asthma severity, only the severe asthma subgroup was used. For data that were split across subgroups and displayed as a percentage (for example proportion of patients with severe asthma and sinusitis across body mass index (BMI) category) each subgroups n's were calculated, added together and percentages recalculated to represent the total for severe asthma participants.

If means and standard deviations were presented in graph form only, numerical values were extracted using GetData Graph Digitizer (16).

Oneway ANOVA with bonferroni pairwise comparisons was calculated for the total number of traits assessed. Paired t-tests were used to calculate the differences between assessed and treated traits, significance levels were set for 0.05.

For the meta-analysis, effect-size estimations for asthma control (asthma control questionnaire, or asthma control test), asthma related quality of life (asthma quality of life questionnaire) and exacerbations were calculated from means and standard deviation when available, or mean data and p-values. Median data were used if mean data were unavailable/not reported, which was considered the best estimator in samples over n = 25 (17). Three outcome studies were included in the meta-analysis (18-20). Exacerbation counts were explicitly reported pre and post intervention in two studies (19, 20). In one study exacerbations were not explicitly reported (18), so number of prednisone doses pre and post intervention were considered to be an exacerbation. All exacerbation effect sizes were calculated from median data, and therefore may provide a more conservative estimate of effect. Effect size was calculated in standardised differences in mean, and 95% confidence intervals. The comparison was pre and post intervention (no control conditions). Effect sizes greater than zero were classified as an improvement in asthma control or asthma related quality of life. An effect size of less than zero was classified as a reduction in exacerbations.

Results

Study Types

A total of 26 studies were included. The included studies were heterogeneous in their design and research questions. For the purpose of this review we allocated the studies to three groups based on their design. The first being “cohort studies/cross sectional studies” (thirteen studies; 21, 22-34), which includes those that used multidimensional assessment to examine the prevalence of comorbidities and risk factors among selected groups of patients with severe asthma. Also included in this group were studies that used baseline variables to predict outcomes, such as exacerbations.

The second group of studies is the “experimental/outcome studies” (six studies; 6, 18-20, 31). These studies employed a multidimensional assessment approach, and reported targeted treatment accordingly, in either an experimental paradigm, or as part of the facility’s routine care clinics.

The final group of studies are the “severe asthma disease registries” (eight registries, from seven studies; 35, 36-41), which provide an overview of severe asthma and its related characteristics.

Participants

The demographic information for the included studies is shown in Table 1. Overall, the mean±SD age of participants across all of the studies was 47.2±5.9 years, with a female predominance (63.6%). The overall age of diagnosis was 17.6±6.9 years and their duration living with asthma was 22.5±7.8 years. Participants were reflective of a severe asthma population in terms of clinical outcomes and medication use; FEV_1 was 69.6%±8.6 of predicted, and participants had a mean of 3.6±1.4 exacerbations in the past year, representing 2.1±1.2 emergency department visits. Participants were prescribed high dose ICS (1639.8±509.7µg per day beclomethasone dipropionate equivalent) and over one quarter (26.8%) were prescribed maintenance oral corticosteroid (OCS).

Assessment: What traits are being measured as part of the multidimensional assessment of severe asthma and its comorbidities?

Airway Components

Cohort studies/cross sectional studies: This category of studies comprises the bulk of the literature on this topic (n=13). As shown in Table 2, bronchodilator reversibility (BDR) and airflow limitation were assessed 12 out of 13 studies (22-25, 27-30, 32-34, 42). Lung structure abnormality, assessed via chest X-ray, or chest computerised tomography (CT) was assessed in six studies (22, 25, 28, 29, 32, 42). Blood eosinophils were assessed in eight studies (21-25, 30, 32-34) and airway inflammation (assessed by induced sputum and cell counts or fractional exhaled nitric oxide (FeNO) in fewer than half (six studies) (23, 25, 27, 30, 32, 33).

Experimental/ outcome studies: BDR and airflow limitation were assessed in all of these six studies (Table 2). Airway inflammation was assessed (either by sputum or FeNO) in all but two studies (18-20, 42). Blood eosinophils were assessed in all of the studies in this cluster apart from Amin et al (31). Lung structure abnormalities were assessed in four (19, 20, 31, 42) and exercise capacity in three of the six studies (19, 20, 42).

Severe asthma disease registries: BDR and airflow limitation were assessed in all registries except for the Optimum Patient Care Research Database (ORCRD) (40). The Belgian Severe Asthma Registry provided the most comprehensive airway assessment, measuring airway inflammation (FeNO and sputum), frequent chest infections, pathogen colonisation, and blood eosinophils (39).

Comorbidities

Cohort studies/cross sectional studies: Psychological dysfunction was the comorbidity that was most frequently assessed (nine out of 13 studies)(24, 25, 27-30, 32, 34, 42), followed by sinusitis (nine studies)(22, 25, 28-30, 32-34, 42) and gastro-oesophageal reflux disease (GORD) (six studies) (22, 24, 29, 30, 32, 34). Immune deficiency, cardiac dysfunction, and systemic inflammation were not commonly assessed (Table 3).

Experimental/outcome studies: All six studies assessed psychological dysfunction and GORD (6, 18-20, 31, 42), and five assessed sinusitis (6, 19, 20, 31, 42)(Table 3). Obstructive sleep apnoea syndrome (OSAS), vocal cord dysfunction (VCD) and cardiac dysfunction were less commonly assessed, and systemic inflammation was assessed in only one study (20).

Severe asthma disease registries: GORD was the most commonly documented comorbidity (Table 3), recorded in six out of the eight registries (37-41). This was followed by sinusitis (35, 37-39, 41) and psychological dysfunction (37, 39, 40), which was documented in 50% of the registries. Cardiac dysfunction and OSAS were also recorded in four of the registry studies (37, 40, 41).

Risk Factors

Cohort studies/cross sectional studies: Atopy and/or IgE and smoking status were the most commonly assessed risk factors (11 studies of 13 studies) (21, 23-30, 32-34). This was followed by BMI and drug sensitivity (22, 24, 25, 28, 29, 32-34), for example sensitivity to aspirin or non-steroidal anti-inflammatory drugs. Non adherence and inhaler device technique were rarely assessed (three (27, 28, 32) and two studies (29, 32) respectively; Table 4).

Experimental/outcome studies: Smoking status was assessed in all studies, followed by atopy, inhaler technique and non-adherence (assessed in five out of six studies) (6, 19, 20, 31, 42). In contrast to the cohort studies, drug sensitivity was only assessed in half the studies (6, 19, 31) (Table 4).

Severe Asthma Disease Registries: Smoking status and atopy were assessed in six out of the eight severe asthma registries. BMI was recorded in just over half of the registries (36-38, 40, 41) and non-adherence was assessed in only one of the registries (40) (Table 4).

Comparison across study types

Study type significantly impacted on number of traits that were assessed as part of MDA. Experimental/outcome studies assessed the most traits overall (16.3 ± 4.9), compared to cohort studies (11.08±4.1) and severe asthma registries (9.0±3.7, p = 0.01). Figure 3 plots the number of traits assessed and treated according to study type. There was a significantly higher number of traits assessed in the “risk factors and self-management domain” overall (p = 0.002) and between the experimental/outcome studies compared to cohort studies, p = 0.01, and severe asthma registries (p = 0.002). However, there were no significant differences between the airway domain, or the comorbidity domain.

The effect of multidimensional assessment

A total of six studies were classified as ‘experimental/outcome studies’ (group 2). The outcomes of the ‘experimental/outcome studies’ ranged from distinguishing difficult to treat

asthma from treatment resistant asthma (6, 32, 42) to improvement in asthma outcomes, including health related quality of life (HRQoL), asthma control, health care usage and lung function measures (18-20). No studies in this cluster were randomised controlled trials (RCTs), or had control comparisons.

Amin et al. (31) conducted a study evaluating a systematic approach to distinguish difficult to treat asthma from non-genuine cases of difficult to treat asthma. They concluded that as a result of their MDA, they were able to classify their patients as non-difficult to treat in 90% of cases. A 2003 study by Heaney et al. (42) that examined a MDA and targeted treatment protocol among a sample of patients with severe asthma concluded that difficult-to-treat and treatment resistant patients both had a high number of comorbidities, and their assessment was not useful in distinguishing these populations. Irwin et al. (6) conducted a MDA and management protocol for the treatment of people with severe asthma, the outcome was reduction in the proportion of participants who were considered to have difficult to treat asthma. They found that their assessment protocol and treatment reduced difficult to treat asthma cases by 74% and further concluded that approximately 2.7 risk factors or comorbidities were responsible for the difficult to treat asthma status. Gibeon et al. (18) assessed the effectiveness of a MDA protocol that was implemented in a specialist severe asthma clinic and concluded that their assessment improved HRQoL and asthma control, while reducing OCS use and healthcare utilisation. Tay et al (19) conducted a structured approach to assessment of difficult asthma within their difficult asthma service. This approach sought to 1) confirm the diagnosis, 2) assess and intervene on contributory factors (non-adherence and comorbidities), and 3) phenotype asthma for targeted biological therapy. The authors concluded that their structured approached significantly reduced number of exacerbations, and improved asthma control. In addition there were improvements in dysfunctional breathing and chronic rhinosinusitis. Similarly, Van der Meer et al., who recruited severe asthma participants and performed a multidimensional assessment conducted by a severe asthma team, found a beneficial effect of multidimensional assessment, with increases in asthma related quality of life and asthma control and decreased health care use (20).

A meta-analysis of three studies was included (18-20). As shown in Figure 2 there were small to medium improvement in the outcomes of asthma control and HRQoL. The mean differences for asthma control and HRQoL were 0.359 and 0.359 respectively. There was a small reduction in exacerbations post intervention with a mean difference of -0.335.

Treatable traits and treated traits

Among the studies classified as experimental/outcome studies, participants had a mean±SD of 5.2±2.0 airway traits assessed, 5.0 ±1.4 comorbidities and 6.2 ±1.9 risk factors. Whilst there was a mean of 5.2 airway traits assessed, significantly less were treated, 3.2±0.8 p = 0.03 (Figure 3). There was no significant difference between the number of comorbidities assessed and treated (5.0 ±1.4 compared to 3.5 ± 2.4), however significantly more risk factors were assessed compared to risk factors treated, (6.2 ±1.9 compared to 3.8 ± 2.0) p = 0.003. The treated risk factors included inhaler device technique, non-adherence and atopy (Table 4).

Follow-up time period

The median follow-up period across all studies was 10 months (IQR; 4.5-16). Amin (31) followed their sample for 3 months and Van der Meer (20) followed up their sample at 6 and 12 months post MDA. Gibeon (18) had a medium follow-up of 10 months and in Heany et al. (42) they was a minimum of 12-months follow-up post assessment. Tay et al. (19) evaluated their intervention 6 months post their initial visit. The follow up period of Irwin et al. (6) was approximately 20 months post initial assessment, and further quantified that it took approximately 1.8 years for people with difficult to control asthma to obtain control, with improvements noted in these patients four months after their protocol was instituted.

Comorbidity and Risk Factor Prevalence

The prevalence of the comorbidities according to individual study is presented in Figure 4. Atopy was the most common risk factor and respiratory infections were the most common comorbidity followed by sinusitis, GORD and obesity. Psychological functioning, which mainly consisted of anxiety and depression were the most commonly assessed comorbidities.

In addition to the comorbidities presented in Figure 4, Schleich et al. (39) reported that 3% of participants had Churg Straus Syndrome, 7% had emphysema and 3% had allergic bronchopulmonary aspergillosis (APBA). The prevalence rate of kidney disease was 14% in the OPCRD registry (40). In addition Bruno et al. (24) reported 2.8% prevalence rate of tuberculosis.

COPD was also assessed as part of the lung function assessment, but its overall prevalence as a coexisting comorbidity was not reported by the majority of studies, with the exception of

Amin et al. (25% prevalence reported) (31) and Gibson et al. (10.2%) (37). Others stated that they excluded COPD patients (24, 28, 32).

Comparison to key recommendations

A number of key publications have proposed the use of MDA in airway diseases including severe asthma (2-4, 12). We have compared the recommendations of four publications (Agusti et al.; Bel et al; Chung et al and Gibson et al) to the traits assessed in the included studies. If the recommendation suggested that a particular trait be assessed and/or treated in severe asthma, they are denoted with a symbol in Tables 2-4. In addition to the traits that have been listed in the tables 2-4, Agusti et al., (3) also suggested that bronchiectasis be assessed, as well as pre-capillary pulmonary hypertension, chronic respiratory failure, cough reflex sensitivity, deconditioning, laryngeal obstruction, side effects of treatments and family and social support. In addition to the traits listed in the tables 2-4 Bel et al. (4) suggested the assessment and treatment of intra-bronchial obstruction, recurrent micro aspiration, cystic fibrosis, ABPA, emphysema, hypersensitivity pneumonitis, pulmonary embolism, pulmonary arterial hypertension, bronchiolitis, bronchiectasis and churg strauss syndrome, although some of these traits would be considered structural abnormalities and therefore would be assessed using chest CT or CXR.

The ERS/ATS guidelines (12) suggest MDA of the airway domain and related comorbidities. They also recommend a number assessments and treatments that should not be considered in the routine assessment and management of severe asthma, for example the use methotrexate and macrolide antibiotics. Assessment and treatment with antifungal agents are recommended in recurrent exacerbations of ABPA. Bronchial thermoplasty is recommended where indicated. FeNO is not recommended in people with severe asthma (12). The recommended traits proposed by Gibson et al. (2) are all listed in Tables 2-4.

Discussion

This systematic review and meta-analysis of multidimensional or systematic assessment in severe asthma has identified several studies that have used MDA in the management of severe asthma, but did not identify any RCTs evaluating its effect. Cohort/cross sectional studies (21-34) have been reported and a number of experimental/ outcome studies have suggested that MDA leads to improved outcomes (6, 18-20). MDA has also been suggested as a method of managing severe asthma by several recent recommendations (2-4, 12). Whilst these recommendations are considered important, there is no consensus on what

should be assessed as part of the MDA, or where treatment should be targeted. The results of this review therefore indicate a need for consensus among relevant stakeholders to define the optimal approach to MDA, followed by clinical trials to establish the efficacy of this approach.

Assessment: What traits are being measured as part of the MDA of severe asthma and its comorbidities?

As has been outlined by this review, there are some traits which are commonly assessed across all of the studies that have employed a MDA approach. These include assessment of BDR, airflow limitation, sinusitis, GORD, psychological functioning, atopic and smoking status. The other traits reported in this review are less consistently assessed between studies. With the exception of the experimental/outcome studies, inhaler device technique, exacerbation management, inhaler polypharmacy and medication adherence were sparsely assessed. This is an interesting finding and one of concern as medication adherence and inhaler technique impact greatly upon the successful treatment of asthma (43) and these traits were included in all of the recommendations of guidelines and opinion leaders (2-4, 12).

Study type determined the comprehensiveness of the assessment. Experimental/outcome studies assessed significantly more traits compared to cohort studies and severe asthma registries. It is not surprising that studies designed to examine the outcome of multidimensional assessment would do a more comprehensive patient assessment, however this does bring into question the generalisability and feasibility of a more comprehensive assessment in a real world setting. For example the data collected by the severe asthma registries, which occurs in the real world clinical setting, assessed only half as many traits on average compared to experimental/outcome studies (9.0 to 16.3 traits). This may highlight a need to consider what traits are feasible to assess, and consider what the best approach is for successful implementation of multidimensional assessment and targeted treatment into current severe asthma management practices.

Blood eosinophils were assessed in over half of the studies (16 studies). Until recently blood eosinophils have not been recommended as a method of targeting airway inflammation (2-4, 12). The role of blood eosinophils in the assessment and management of airway disease is currently the focus of investigation (44, 45) with studies suggesting a high degree of correlation between this measure and sputum eosinophil counts (46). Blood eosinophils are now also recommended as the biomarker to select patients for targeted therapies such as mepolizumab (47), as the treatment is more responsive in patients with a blood eosinophil count of ≥300 cells/μL or ≥0.3 x 10^9 cells/L (47). These new data have emerged since the

publication of earlier recommendations (2, 4, 12) and as such recommendations regarding the use of blood eosinophils are likely to change (48).

Assessment of airway inflammatory profile is currently recommended by three of the recommendations (2, 3, 12), although not widely used in the reviewed studies. This discordance between the relatively low use of the induced sputum or FeNO among studies (50%), compared to strong consensus of the recommendations suggests that these measures are not easily implemented into practice, outside specialist asthma clinics. This creates an opportunity to either make this technology more accessible for clinicians in private practice or the general practice setting, or to use a different biomarker to target treatment of airway inflammation. It should be noted that Chung et al. specifically states that FeNO is not recommended to titrate treatment in severe asthma (12). Further work is underway in this area, the United Kingdom Refractory Asthma Stratification Program (UK RASP) is currently assessing the validity of a composite measure to titrate OCS dose, using periostin, FeNO and blood eosinophils (49). This may be a feasible alternative to sputum induction.

The effect of multidimensional assessment

The majority of studies in this review used MDA to characterise severe asthma. When MDA was used to drive treatment decisions, MDA was credited with increases in HRQoL and asthma control (18-20), reduction in the number of difficult-to-treat asthma cases (6), identification of previously unknown, but impactful comorbidities, and usefulness in identifying severe asthma phenotypes that can be targeted with biological therapies (19). Multidimensional assessment was not, however, deemed to be useful for the differentiation between treatment refractory asthma and difficult-to-treat asthma (42). Though the distinction between these two subtypes of severe asthma may be less important under a proposed targeted therapy (2) “treatable traits” model, (3) where treatment is targeted to specific traits, and not based on diagnostic labels.

Untreated traits

Among the experimental/outcome studies, there were significantly more traits assessed than were treated. On average 5.2 traits assessed to 3.2 traits treated for the airways domain, and 6.2 risk factors assessed to 3.8 risk factors treated. This indicated that clinicians are prioritising treatment to specific traits, for example BDR, airflow limitation and airway

inflammation were in most cases treated. In addition, inhaler device technique, adherence and IgE were also treated in most cases. In contrast, the airway traits of pathogenic colonisation, lung structure abnormalities or blood eosinophils were rarely or not explicitly treated. Lung structure abnormalities in this assessment included diseases that could be diagnosed on a chest CT scan, or a chest X-ray. In some cases treatment of these abnormalities may not be possible, which is an important consideration to the "treatable traits" model proposed by Agusti et al. (3) where if it is a 'non treatable trait', is there any need to assess it?

Time to successful treatment

The median follow-up period across the studies was 10 months. Most of the outcome studies included in this review were able to detect beneficial treatment outcomes within that time frame. Irwin et al. (6) and Amin (31) stated that improvements could be noted in their patients as early as three to four month post the implementation of their MDA and targeted treatment protocol. Irwin et al. (6) further quantified that it took approximately 1.8 years for difficult to treat asthma patients to be no longer classified as difficult-to-treat. These follow-up times are important considerations when determining the effectiveness of a MDA approach, particularly in light of government funded treatment programmes. For example the Australian Pharmaceutical Benefits Scheme allows a period of 24 and 30 weeks to assess initial response to funded omalizumab and mepolizumab respectively. This does, however follow a requirement that the patient has their severe asthma optimised for at least 12 months prior to treatment in order to be eligible. In the RCTs that evaluated the efficacy of these targeted severe asthma therapies the treatment periods were 32 weeks for omalizumab (50) and 52 weeks for mepolizumab (47). Whilst this may be enough time to note improvements in some severe asthma outcomes (including asthma control and quality of life), a longer follow-up may be required to detect improvements in other areas.

Comorbidities and risk factor prevalence

Comorbidities and risk factors are highly prevalent among those with severe asthma and adversely impact exacerbations frequency, asthma control, and HRQoL (51). There are several comorbidities that are associated with severe asthma, which we found to be high in prevalence (atopy, recurrent respiratory infections, sinusitis, GORD, anxiety and depression) (22, 25-28, 31, 37, 40, 42). There was high variability for comorbidity prevalence across studies (supplementary table 1). For example, the prevalence of VCD ranged from 1.6% to 33% across five studies (19, 22, 31, 32, 37). The same variability between studies is noted for OSAS, with the prevalence ranging from 4% to 40.3% (18-20, 24, 29-32, 34, 40, 41). This variation may occur if the studies included in the review were not necessarily designed to

characterise comorbidities, so differences in diagnosis technique and diagnostic thresholds may have been used between studies (e.g. comorbidities may have been assessed via self-report). A range of comorbidities, including those of high prevalence that are known to impact adversely on severe asthma, including BMI, GORD, OSAS, dysfunctional breathing and VCD (51) should be considered as part of a multidimensional assessment.

COPD was inconsistently assessed, two studies reported the prevalence rates of COPD among a severe asthma population (31, 37). Heaney et al. assessed and managed COPD as part of their MDA and intervention, but COPD was an exclusion criteria in other studies (24, 28, 32). Asthma and COPD overlap has a recently been examined within a severe asthma population using data from a severe asthma omalizumab register (37), the present authors report that biological therapies designed for severe asthma show a beneficial effect in severe asthma and COPD overlap (52). Similarly, long-acting anti-muscarinic antagonists such as tiotropium are also beneficial for severe asthma (53, 54). This highlights an important consideration for the place of COPD in the MDA of severe asthma (55).

Consensus

Airflow limitation, psychiatric comorbidities (mainly anxiety and depression), sinusitis and smoking status were all commonly recommended and assessed across both the studies and the recommendations of guidelines and key opinion leaders. Atopy, OSAS and GORD were assessed by majority of studies. As previously mentioned, adherence and inhaler technique was recommended by all of the recommendations and only assessed by approximately one quarter of the included studies. Of note, while psychiatric comorbidities are commonly assessed, few treatment interventions, if any, exist to target anxiety and depression specifically in a severe asthma population. Anxiety and depression impact negativity on quality of life but also on medication adherence (56), which can lead to adverse outcomes for those with severe asthma. This overall discordance between what is being assessed, treated and recommended for treatment highlights a path for future research and future action by policy makers.

Limitations

The focus of this review, and therefore the associated search criteria, was to provide an overview of studies that have conducted a MDA of severe asthma. A major challenge was the conversion of this abstract concept into concrete search terms for a systematic review. We aimed to address this challenge by conducting searches with a range of terms (i.e.

multidimensional, systematic, precision medicine etc.). However, we acknowledge that many studies which perform “multidimensional” assessment may not use these specific key terms and would have been missed in our search.

Similarly, we noted that the search did not capture all severe asthma registry manuscripts, which are likely to have included MDA. However, within the context of severe asthma registries while multidimensional data is typically collected it is rarely used to inform disease management. Registry studies which reported multidimensional assessment (as per our “assessment” search terms) were captured in our search strategy.

Further, some traits that may have been assessed and/or treated as part of routine clinical practice may not have been reported by the included studies and therefore not captured in this systematic review. However, whilst the list of assessed and treated traits may not be inclusive of every trait assessed and treated, it does provide an overall snapshot as to what is being commonly assessed and treated in this study.

The primary goal of this review was to assess the effectiveness of multidimensional assessment. Our search identified a limited number of studies which examined the effectiveness of multidimensional assessment. Only six studies were considered to be experimental/outcome studies and none of these studies had control comparisons. This highlights the importance of well-designed clinical trials that test the approach of multidimensional assessment and targeted therapies for severe asthma, however despite the need for these studies, the overall conclusion are in favour of its usefulness among a severe asthma population.

Conclusions

Multidimensional assessment appears to be a useful approach for the management of severe asthma. It accounts for the heterogeneity in severe asthma which stems from several underlying phenotypes that can be impacted by several comorbidities and risk factors. Whilst there was some inconsistency between studies among what traits are assessed, there were some traits that were commonly assessed across all studies. Further, whilst comorbidities and risk factors in severe asthma are frequently assessed, they are treated less frequently. To address this, consensus is needed on what traits should form the basis of a MDA, what traits treatment should target, and what model of care should be used to implement this approach.

One limitation of the current literature published in this area is the lack of RCTs. These are essential for examining the efficacy of the MDA approach. Further, when designing new studies, it should be noted that the MDA approach takes minimum of 4 months for effects to become apparent, and longer for severe asthma to become controlled.

The experimental/outcome studies included in this systematic review were useful in determining initial success of MDA, but without a control comparison, it is difficult to make firm conclusion as to its effectiveness as compared to routine care.

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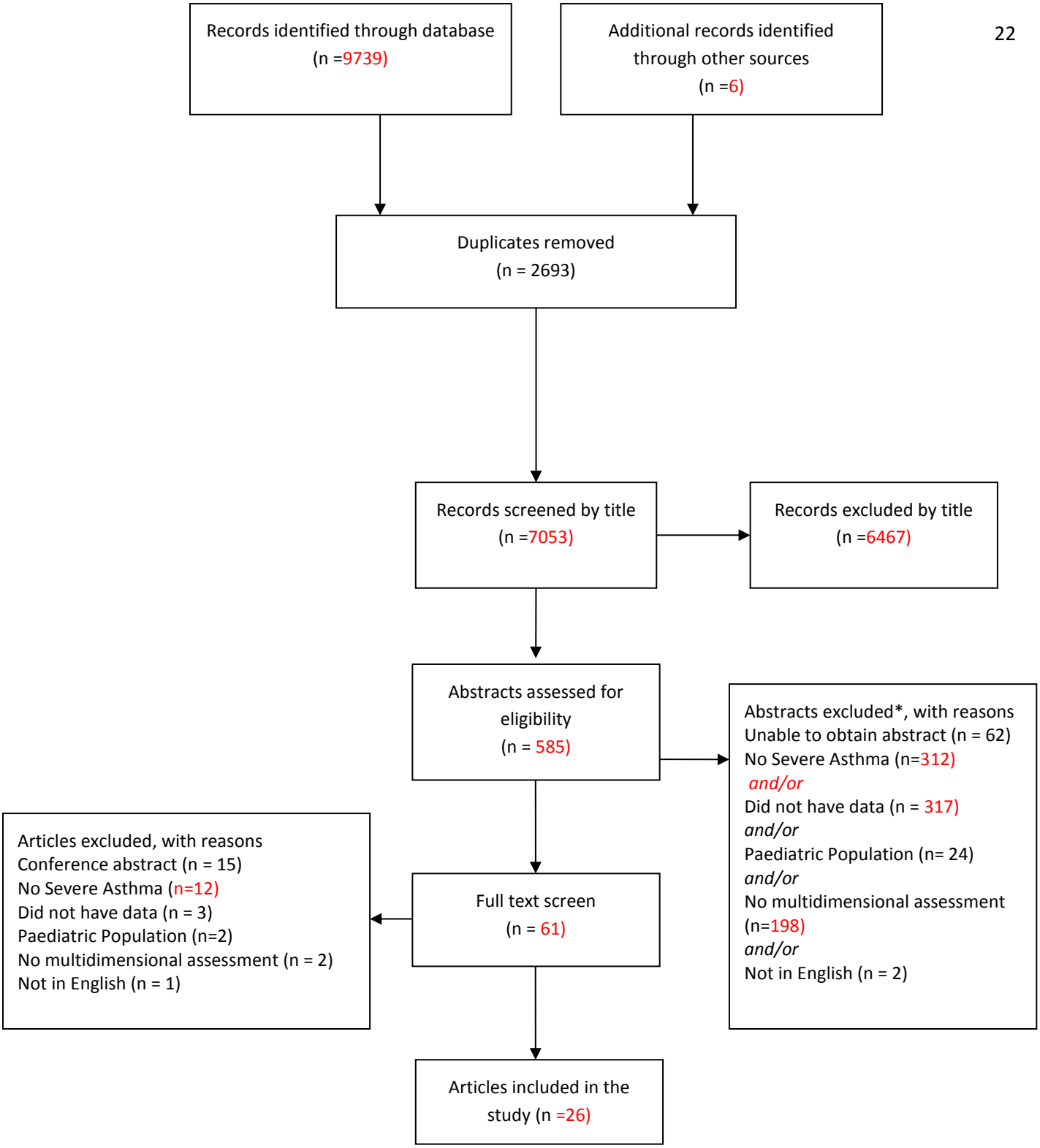


Figure 1: CONSORT study selection process for the systematic review examining multidimensional assessment in patients with severe asthma

*some articles were overlapping in the exclusion criteria

Table 1: Available Baseline demographics of the studies included in the systematic review

Study	n	Age (years)	Gender (% female)	Age of Onset (years)	Asthma Duration (years)	Dose of ICS (µp BDP^)	Maintenance OCS* (%)	Baseline FEV_1 (% predicted)	Reversibility FEV_1 change	Exac. Past Year (n)	ED⁺ Visits (n)	Quality Rating
Cohort/ Cross Sectional Study												
Al-Dorzi et al., (2014)	30	37.5	30				13.6				3.5	Poor
Bisaccioni et al., (2009)	245	57.8	79.2				2.5	60				Fair
Brasier et al., (2010)	461		61.3	14				65				Good
Bruno et al., (2014)	102	56.2	56.7		26.7			61.27		2.3		Fair
De Carvalho-Pinto et al., (2012)	74	44.5	77	9	31.5	1394	20	54				Fair
Heaney et al., (2005)	65	43.8	68	22.7	21.1	2406	29.2	71		4.3	0.82	Good
Kardos et al., (2011)	572	47.5	61.4		16.9			85	3.1	2.53	1.06	Good
Kimura et al., (2017)	127	58.0	59.8		19.8	1649	35.4	91.4				
Radhakrishna et al., (2016)	90	52	58		30	864		67				Fair
Robinson et al., (2003)	55	36	74.5					63.6				Fair
Ten Brinke et al., (2005)	137	45.4	69.9	16.5	18	1600	32.6	72.9	11.6	4	2	Fair
Van Veen et al., (2008)	136	46.1	72.05	12.5	22	1600	32	80.85				Fair
Yii et al.,2017	177	56	53.7	33				68.4				
Experimental/ Outcome Study												
Amin et al., (2014)	200	41.6	70	8.9	18	1500	10					Fair
Gibeon et al., (2015)	346	46	66.7	16		2000	41.2	72	7		4	Fair
Heaney et al., (2003)¤	73	42.6	67	22	20.6	2347	28.8	72		4.3	0.85	Good
Irwin et al., (1993)	42	48	54.8		15.1			69				Fair
Tay et al., (2017)	65	54	63.1	24	31	897	20	65		2¯	2¯	
Van der Meer et al., (2016)	40	51	65			750	28	80		4.5	3	Good
Severe Asthma Registry												
Braunstahl et al. (2011)	294	46.1	62.9		18.8	1590.1	28.2	62.4		4.4	1.3	Good
Denlinger et al. (2017)#	522	49.6	60’		20.6’		11’					
Dolan et al. (2004)	3489	48.9	71.2					74.2	4.8			Fair
Gibson et al. (2016)	180	51.4	63.3			2000	52	64				Good
Moore et al. (2007)	204	41	64	16	25		32	62				Good
Schleich et al. (2014)	350	55	57			2000	24	68	11	2.03	0.95	Fair
Sweeney et al., (2016)												Fair
BTS	770	50	65	16		2000		71.27		4	4	
ORCRD	808	49	63									

^BDP -beclometasone dipropionate * OCS- Oral corticosteroid; ⁺ Past Year. ¤Heaney et al (2005) was classified as cohort/cross sectional study as Heaney et al (2003) reported the original outcome of the multidimensional assessment and the two studies are drawn from the same study sample.# Adult sample only unless otherwise indicated; ‘ including an additional (n =161) children and adolescents ¯Past 6 months

Table 2: Airways components commonly assessed in the studies that were included in this systematic review

Study	Bronchodilator Reversibility	Exercise Capacity	Airflow Limitation	Airway inflammation		Frequent Chest Infections	Pathogen Colonisation	Mucus Hypersecretion	Lung Structure Abnormality	Oxygen Desaturation	Blood Eosinophils
Recommended	α ∪	∪ Ɣ α	∪ Ɣ † α	∪ Ɣ α		∪ Ɣ †	∪ Ɣ	Ɣ	† α	Ɣ	
				FeNO	**Sputum**						
Cohort/Cross Sectional Studies											
Al-Dorzi et al. (2014)						x				x	x
Bisaccioni et al. (2009)	x		x						x	x	x
Brasier et al. (2010)	x		x		x						x
Bruno et al. (2014)	x		x								x
De Carvalho-Pinto et al. (2012)	x		x	x	x				x		
Heaney et al. (2005)	x		x						x		
Kardos et al. (2011)	x		x	x	x						
Kimura et al., (2017)	x		x	x	x						x
Radhakrishna et al. (2016)	x		x	x					x		x
Robinson et al. (2003)	x	x	x					x	x		
Ten Brinke et al. (2005)	x		x			x			x		
Van Veen et al. (2008)	x		x	x	x	x					x
Yii et al.,2017	x		x								x
Experimental/Outcome Studies											
Amin et al. (2014)	x +		x +						x		
Gibeon et al. (2015)	x +		x +	x +							x
Heaney et al. (2003)	x +	x +	x +		x		x		x +		x
Irwin et al. (1993)	x +		x +								x
Tay et al., (2017)	x +	x	x +	x +				x +	x		x
van der Meer et al. (2016)	x +	x	x +	x +	x +				x		X
Severe Asthma Registries											
Braunstahl et al. (2011)	x		x								
Denlinger et al. (2017)	x		x	x	x						x
Dolan et al. (2004)	x		x								
Gibson et al. (2016)	x		x						x		
Moore et al. (2007)	x		x	x		x					x
Schleich et al. (2014)	x		x	x	x		x				x
Sweeney et al. (2016)											
BTS	x		x						x		
ORCRD											

x Assessed **+** Treated ∪ Agusti et al.; Ɣ Gibson.; † Bel et al.; α Chung et al; FeNO- Fractional Exhaled Nitric Oxide

Table 3: Comorbidities commonly assessed in the studies that were included in this systematic review

Study	GORD	Anaemia	Psych	Cardiac	Dysf. Breathing	Systemic Inflam.	Immune Deficiency	VCD	Sinusitis	Obstructive Sleep Apnoea
	ʊ † α	ɣ	ʊ ɣ † α	ʊ ɣ † α	ʊ ɣ † α	ʊ ɣ †		ʊ † α	ʊ † ɣ α	ʊ † α
Cohort/ Cross Sectional Study										
Al-Dorzi et al. (2014)										
Bisaccioni et al. (2009)	x							x	x	
Brasier et al. (2010)										
Bruno et al. (2014)	x		x	x						x
De Carvalho-Pinto et al. (2012)			x						x	
Heaney et al. (2005)			x						x	
Kardos et al. (2011)			x							
Kimura et al., (2017)						x			x	
Radhakrishna et al. (2016)	x		x	x	x			x	x	x
Robinson et al. (2003)		x	x		x	x		x	x	
Ten Brinke et al. (2005)	x	x	x		x		x		x	x
Van Veen et al. (2008)	x		x			x			x	x
Yii et al.,2017	x		x						x	x
Experimental/Outcome Study										
Amin et al. (2014)	x +		x					x	x +	x
Gibeon et al. (2015)	x +	x +	x +							
Heaney et al. (2003)	x +		x +		x +			x +	x +	
Irwin et al. (1993)	x +		x +	x +					x +	
Tay et al., (2017)	x +		x +	x +	x +			x +	x +	x +
Van der Meer et al. (2016)	x		x		x	x			x	x
Severe Asthma Registry										
Braunstahl et al. (2011)									x	
Denlinger et al., (2017)	x			x					x	x
Dolan et al. (2004)										
Gibson et al., (2016)	x		x	x	x			x	x	x
Moore et al., (2007)	x								x	
Schleich et al. (2014)	x		x						x	
Sweeney et al. (2016)										
BTS	x		x	x						x
ORCRD	x		x	x						x

VCD – Vocal Cord Dysfunction; GORD- Gastric Oesophageal Reflux Disease; Dysf. Breathing- Dysfunctional Breathing; Systemic Inflam.- Systemic Inflammation; **x** Assessed **+** Treated ʊ Agusti et al.; ɣ Gibson.; † Bel et al.; α Chung et al.

Table 4: Risk factors and self-management skills commonly assessed in the studies that were included in this systematic review

Study	Exacerbation Management/ Action Plan	Inhaler Device Polypharmacy	Inhaler Device Technique	Non Adherence	Smoking Status	Atopy/ IgE	BMI	Sarcopenia/ Cachexia	Bone Density	Hormonal/ Environmental/ Sensitiser Exp[α]	Drug Sensitivity
	ɣ	ʊ ɣ	ʊ ɣ † α	ʊ ɣ † α	ʊ ɣ α	† α	ʊ ɣ † α	ʊ	ɣ	ʊ † α	† α
Cohort/Cross Sectional Studies											
Al-Dorzi et al. (2014)					x	x					
Bisaccioni et al. (2009)											x
Brasier et al. (2010)						x					
Bruno et al. (2014)					x	x	x				x
De Carvalho-Pinto et al. (2012)					x	x	x			x	x
Heaney et al. (2005)					x	x		x			
Kardos et al. (2011)				x	x	x	x				
Kimura et al., (2017)					x	x	x				x
Radhakrishna et al. (2016)	x		x	x	x	x	x				
Robinson et al. (2003)				x	x	x					x
Ten Brinke et al. (2005)	x		x		x	x				x	x
Van Veen et al. (2008)					x	x	x				
Yii et al., (2017)					x		x				x
Experimental/ Outcome Studies											
Amin et al. (2014)			x +	x +	x					x	x +
Gibeon et al. (2015)					x	x +	x				
Heaney et al. (2003)	x +	x +	x +	x +	x	x +		x		x +	
Irwin et al. (1993)			x +	x +	x +	x				x	x
Tay et al., (2017)	x +		x +	x +	x	x +	x			x	x
Van der Meer et al. (2016)	x +		x +	x +	x	x +	x			x +	
Severe Asthma Registries											
Braunstahl et al. (2011)					x	x					
Denlinger et al., (2017)					x	x	x				
Dolan et al. (2004)					x	x	x			x	
Gibson et al.,						x	x		x		
Moore et al., (2007)					x	x					x
Schleich et al. (2014)					x	x	x			x	
Sweeney et al. (2016)											
BTS				x	x		x		x		
ORCRD											

[α] Menstrual Asthma, environmental trigger exposure, sensitiser exposure. **x** Assessed **+** Treated ʊ Agusti et al.; ɣ Gibson; † Bel et al; α Chung et al.

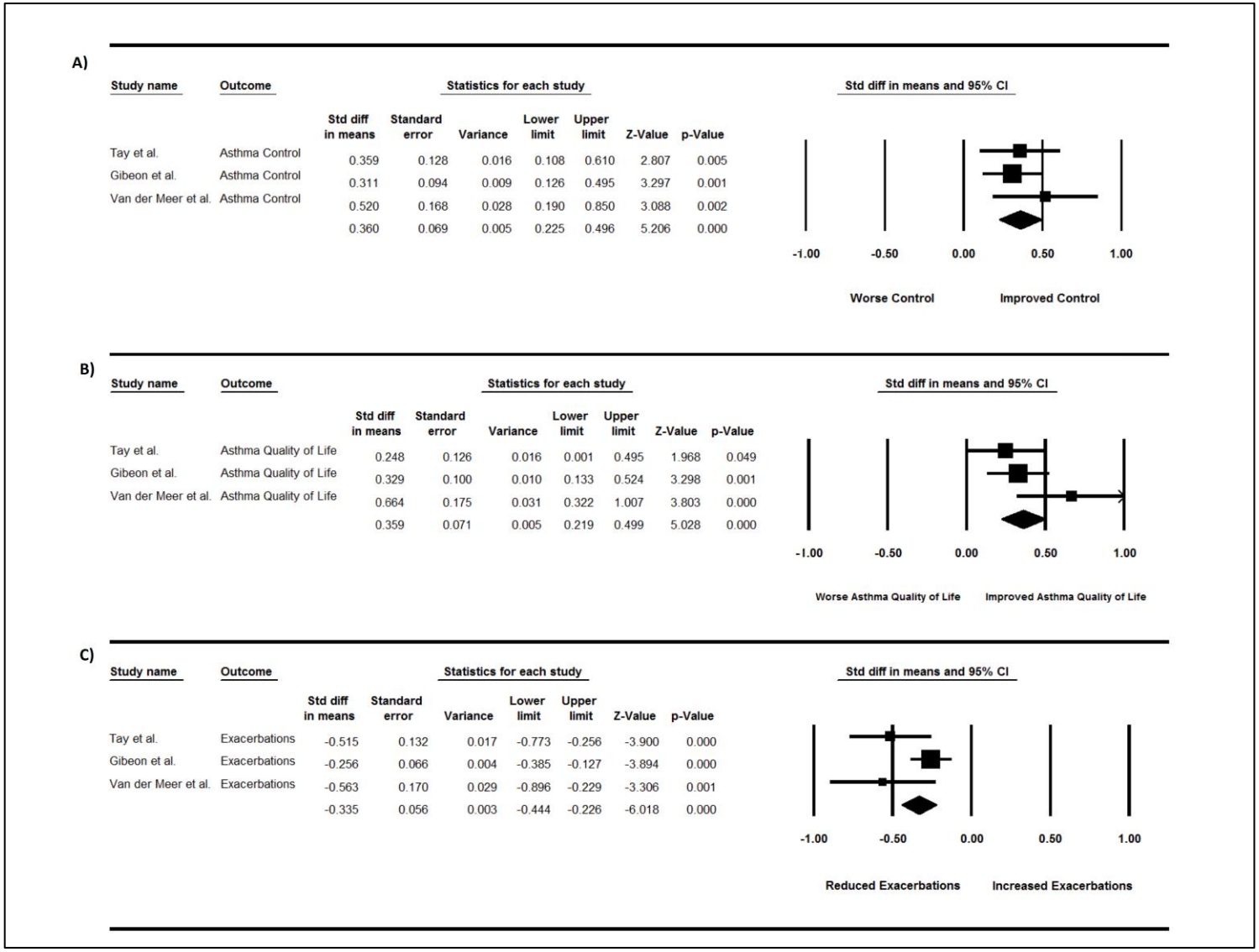


Figure 2: Forest plot of standardized mean difference (95% confidence intervals) for **A) asthma related quality of life**; **B) asthma control** and **C) Exacerbations**, pre and post multidimensional assessment and targeted treatment. A positive effect size indicates an improvement in asthma control or asthma related quality of life. A negative effect size indicates a reduction in exacerbations. The pooled effect size is provided as the black diamond at the bottom of the figure.

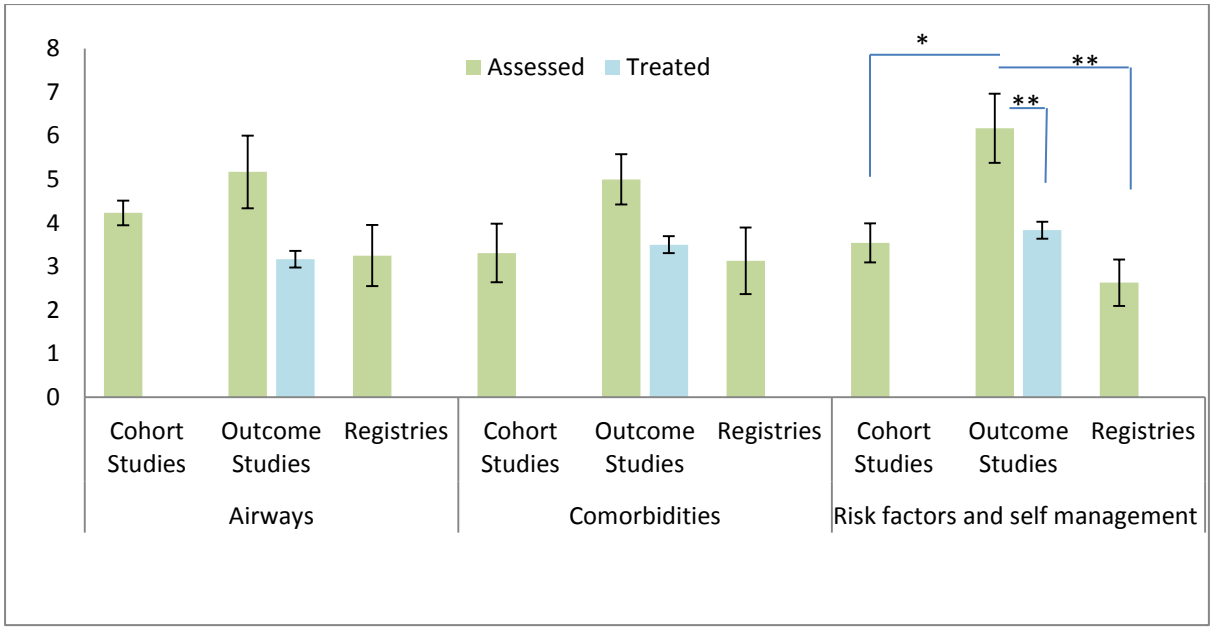
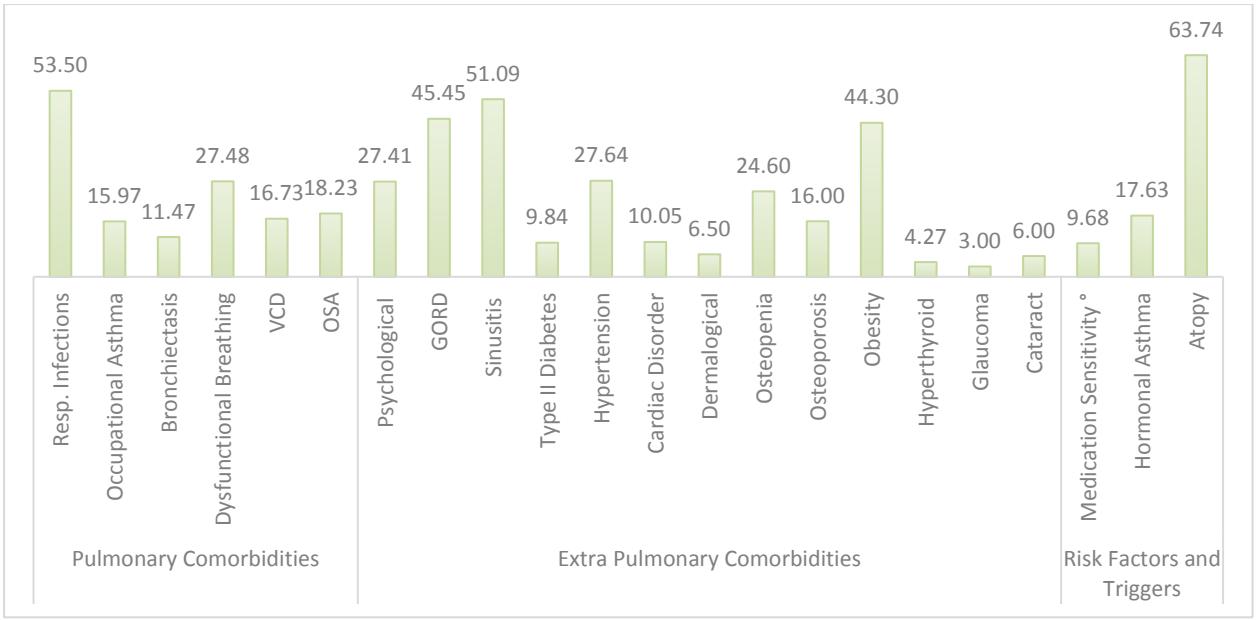


Figure 3: Average number of traits assessed and treated. The number of airways, comorbidity and risk factors domain traits assessed across different study types and the number of traits treated in the experimental/outcome studies. Data represented as mean±SEM, * $p < 0.05$, ** $p< 0.01$.



°NSAID, aspirin; OSA- Obstructive Sleep Apnoea; VCD-Vocal Cord Dysfunction; GORD- Gastric Oesophageal Reflux Disease

Figure 4: The average percentage of comorbidity prevalence across the studies.