DR SARAH A HILES (Orcid ID : 0000-0002-2723-2798)

Article type : Original Article-Asthma and Rhinitis

Working while unwell: Workplace impairment in people with severe asthma

Authors:

Sarah A Hiles[1], Erin S Harvey[1,2], Vanessa M McDonald[1], Matthew Peters[3], Philip Bardin[4], Paul N Reynolds[5], John W Upham[6,7], Melissa Baraket[8], Zaheerodin Bhikoo[9], Jeffrey Bowden[10], Ben Brockway[11], Li Ping Chung[12], Belinda Cochrane[13,14] , Gloria Foxley[15], Jeffrey Garrett[16], Mark Hew[17], Lata Jayaram[18,19], Christine Jenkins[3,20,21,22], Constance Katelaris[14,23], Gregory Katsoulotos[24], Mariko S Koh[25,26], Vicky Kritikos[27,28], Marina Lambert[29], David Langton[30,31], Alexis Lara Rivero[24], Guy B Marks[15,32], Peter G Middleton[33,34,35], Aldoph Nanguzgambo[29], Naghmeh Radhakrishna[17], Helen Reddel[28], Janet Rimmer[15,36], Anne Marie Southcott[19], Michael Sutherland[37], Francis Thien[38], Peter AB Wark[1,2], Ian A Yang[39,40], Elaine Yap[16] , Peter G Gibson[1,2]

Affiliations:

1. Centre of Excellence in Severe Asthma and Priority Research Centre for Healthy Lungs, Faculty of Health, University of Newcastle, Callaghan, NSW, Australia.
2. Department of Respiratory and Sleep Medicine, John Hunter Hospital, New Lambton Heights, NSW, Australia.
3. Department of Thoracic Medicine, Concord Hospital, Concord, NSW, Australia.
4. Lung and Sleep Medicine, Monash University and Medical Centre, Clayton, VIC, Australia.
5. Lung Research, Hanson Institute and Department of Thoracic Medicine, Royal Adelaide Hospital, Adelaide, SA, Australia.

6. Department of Respiratory Medicine, Princess Alexandra Hospital, Woolloongabba, QLD, Australia.
7. The University of Queensland Diamantina Institute, Woolloongabba, QLD, Australia.
8. Department of Respiratory Medicine, Liverpool Hospital School of Medicine, UNSW Sydney, Liverpool, NSW, Australia.
9. Respiratory Department, Waikato Hospital, Hamilton, New Zealand.
10. Department of Respiratory, Allergy and Sleep Medicine, Flinders Medical Centre, Bedford Park, SA, Australia.
11. Department of Medicine, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand.
12. Department of Respiratory Medicine, Fiona Stanley Hospital, Murdoch, WA, Australia.
13. Department of Respiratory and Sleep Medicine, Campbelltown Hospital, Campbelltown, NSW, Australia.
14. School of Medicine, Western Sydney University, Campbelltown, NSW, Australia.
15. Woolcock Institute of Medical Research, Glebe, NSW, Australia.
16. Respiratory Department, Middlemore Hospital, Auckland, New Zealand.
17. Difficult Asthma Clinic, Allergy, Asthma & Clinical Immunology, Alfred Health, Melbourne, VIC, Australia.
18. Department of Medicine, Melbourne Clinical School, University of Melbourne, Melbourne, VIC, Australia.
19. Department of Respiratory and Sleep Disorders Medicine, Western Health, Footscray, VIC, Australia.
20. Concord Clinical School and Respiratory Discipline, University of Sydney, Concord, NSW, Australia.
21. The George Institute for Global Health, Newtown, NSW, Australia.
22. Respiratory Medicine, UNSW Sydney, Liverpool, NSW, Australia.
23. Immunology Department, Campbelltown Hospital, Campbelltown, NSW, Australia.
24. St George Specialist Centre, Sydney, NSW, Australia.
25. Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Singapore.
26. Duke - National University Singapore Medical School, Singapore.
27. Woolcock Institute of Medical Research, Quality Use of Respiratory Medicines, Glebe, NSW, Australia.
28. Department of Respiratory Medicine, Royal Prince Alfred Hospital, Camperdown, NSW, Australia.
29. Respiratory Services, MidCentral Health, Palmerston North Hospital, Palmerston North, New Zealand.
30. Faculty of Medicine, Nursing and Health Sciences, Monash University, Clayton, VIC, Australia.
31. Department of Thoracic Medicine, Frankston Hospital, Frankston, VIC, Australia.
32. South Western Sydney Clinical School, UNSW Sydney, Liverpool, NSW, Australia.
33. Sydney Medical School, University of Sydney, Camperdown, NSW, Australia.

34. Ludwig Engel Centre for Respiratory Research, Westmead Institute of Medical Research, Westmead, NSW, Australia.
35. Department of Respiratory and Sleep Medicine, Westmead Hospital, Westmead, NSW, Australia.
36. St Vincent's Clinic, Darlinghurst, NSW, Australia.
37. Department of Respiratory and Sleep Medicine, Austin Hospital, Heidelberg, VIC, Australia.
38. Department of Respiratory Medicine, Eastern Health and Monash University, Box Hill, VIC, Australia.
39. The Prince Charles Hospital, Metro North Hospital and Health Service, Chermside West, QLD, Australia.
40. UQ Thoracic Research Centre, Faculty of Medicine, The University of Queensland, Chermside, QLD, Australia.

Corresponding author: Peter G Gibson, Hunter Medical Research Institute, Lot 1 Kookaburra Circuit, New Lambton Heights NSW, 2305, Australia.
Peter.Gibson@hnehealth.nsw.gov.au

Running title: Work impairment in severe asthma

Word count:

Abstract: 300

Main text: 3618, excluding tables and reference list.

Figure/table count: 7

Online supplement: Yes

Abstract

Background: Severe asthma affects quality of life; however, its impact on workplace productivity is poorly understood.

Objective: To compare workplace productivity – absenteeism and presenteeism – and impairment in daily activities in severe and non-severe asthma over time and identify characteristics associated with presenteeism in severe asthma.

Methods: The Severe Asthma Web-based Database (SAWD) is an ongoing observational registry from Australia, New Zealand and Singapore. At April 2017, 434 patients with severe asthma and 102 with non-severe asthma were enrolled (18 to 88 years; 59% female). Participants provided comprehensive clinical and questionnaire data at baseline and were followed-up every 6 months for 24 months. Absenteeism (percentage of time not at work), presenteeism (self-reported impairment at work) and impairment in daily activities outside work due to health problems in the last week were calculated.

Results: At baseline, 61.4% of participants with severe asthma and 66.2% with non-severe asthma under 65 years were employed. At younger ages (30-50 years), fewer severe asthma participants were employed (69% vs 100%). Presenteeism and impairment in daily activity were more frequently reported in severe asthma and in participants with poorer asthma control, poorer lung function and more past-year exacerbations (p<0.01). Over time, deteriorating asthma control was associated with increasing presenteeism. Although absenteeism was not different between severe and non-severe asthma, worse asthma control was associated with absenteeism (p<0.001). In participants with severe asthma, presenteeism was reported more frequently in those with poorer asthma control, poorer asthma-related quality of life and symptoms of depression or anxiety (p<0.01).

Conclusion and clinical relevance: Severe asthma was associated with impairment at work and outside the workplace. Improving asthma control and mental health may be important targets for optimising workplace productivity in severe asthma. Presenteeism and absenteeism may represent key metrics for assessing intervention efficacy in people with severe asthma of working age.

Keywords: Severe asthma; registry; workplace productivity; presenteeism; absenteeism; work disability.

Introduction

Severe asthma is a high impact disease that is often refractory to inhaled therapy. It affects up to 10% of patients with asthma yet accounts for most of the disease burden.[1] Recognised impacts of severe asthma include asthma exacerbations, poor health status and poor health-related quality of life,[2,3] which are likely to lead to impaired functioning at work and in other roles. Impairment at work – where illness impairs ability to work – may be associated with negative consequences over time, including extended sick leave, continued health impairment and greater healthcare utilisation, reduced work team cohesion, arrested work progression, reduced earnings, job insecurity and job loss.[4–7] To date there are scant data on the extent and determinants of workplace impairment in severe asthma. Quantifying workplace impairment can provide an understanding of the impact of severe asthma on the lives of patients and represents a crucial step for developing strategies to maximise workplace participation.

Most previous studies on workplace impairment in severe asthma report work absence yet fail to examine the potentially more widespread problem of presenteeism.[8,9] Presenteeism is defined as working at suboptimal capacity because of ill health. Compared to absenteeism, which is partial or complete absence from work due to illness, presenteeism is a relatively new indicator of workplace impairment.[10,11] Presenteeism is often underestimated yet is costly to the economy[12–14] and is associated with an increased risk of absenteeism in the future.[4]

The aim of this study was to quantify the impact of severe asthma on workplace productivity, by comparing absenteeism, presenteeism and impairment in daily activities over time in people with severe and non-severe asthma. The study also examined characteristics associated with presenteeism among people with severe asthma.

Methods

Study design

The Severe Asthma Web-based Database (SAWD) is an observational registry of patients enrolled through centres of the Australasian Severe Asthma Network (ASAN), which includes hospital-based severe asthma and respiratory clinics and private respiratory practices. SAWD comprises a cross-sectional observational study, a prospective cohort study and databank. Participating centres submit anonymised data to the web-based database where data is stored securely using REDCap electronic data capture tools[15] hosted at the Hunter

Medical Research Institute, Australia. REDCap forms were modified from those initially developed by the Alfred Difficult Asthma Service, Melbourne.[16]

SAWD is conducted in accordance with the International Conference on Harmonisation Good Clinical Practice standards and the Declaration of Helsinki, and under the governance framework of the Thoracic Society of Australia and New Zealand. Ethical approval was obtained from relevant national, regional or local human research ethics committees or institutional review boards, according to country-specific requirements (Australia: HNEHREC 12/11/21/4.04, HREC/13/RAH/379, Alfred Hospital EC 391/13, HREC [Tasmania] Network H0014915 and SCGH HREC 2015-133; New Zealand: HDEC 12/CEN/69; and Singapore: SingHealth CIRB 2016/2550). All patients provided informed written consent prior to participating.

The detailed SAWD protocol is available on the Centre of Excellence in Severe Asthma website (http://www.severeasthma.org.au/tools-resources/toolkits/).

Participants

Adult patients with severe refractory asthma and a comparison group with non-severe controlled asthma were enrolled in the registry by staff at 26 centres in Australia, New Zealand and Singapore. Enrolment commenced in August 2013. The current study reports on patients enrolled until April 2017.

To be included in the registry, all patients required a confirmed asthma diagnosis with evidence of variable airflow limitation documented at baseline or during the previous 10 years. Patients were excluded if they were pregnant; had cognitive impairment that prevented completion of data collection forms; were highly dependent on medical care; had significant life limiting co-morbidity; had primary diagnosis of lung disease other than asthma; had current lung cancer or other blood, lymphatic or solid organ malignancy; were unable to attend study visits; and had current exacerbation at the baseline visit.

Patients were classified as having severe asthma if they met the European Respiratory Society (ERS)/American Thoracic Society (ATS) taskforce definition, where control is not achieved despite high level recommended treatment (refractory asthma and corticosteroid-

resistant asthma) or where control can be maintained only with the highest level of recommended treatment.[2] Inclusion criteria for the severe asthma group were optimised management skills (inhaler technique, education, adherence, written asthma action plan); appropriate assessment and management of triggers and relevant comorbidity; use of maximal inhaled corticosteroid (ICS) therapy according to the Global Initiative for Asthma (GINA)[17] guidelines (> 1000µg beclomethasone equivalent) with a second controller (long acting beta agonist [LABA], long acting anti-muscarinic antagonist [LAMA], oral corticosteroid (OCS) ≥ 50% of the previous year, montelukast or theophylline); and meeting at least one definition of uncontrolled asthma[2] (Online Supplement Table S1).

Inclusion criteria for the non-severe asthma group were use of maintenance inhaled controller therapy; asthma control defined as either Asthma Control Questionnaire 6-item (ACQ6)[18] ≤ 1.5 or Asthma Control Test (ACT)[19] ≥ 20; and stable disease with no respiratory infection, asthma exacerbation or change in maintenance therapy in the four weeks preceding screening.

Data collection and assessments

Clinical and patient-reported data were collected via face-to-face visits, telephone and mail at baseline and at 6-month intervals for 2 years. At the baseline assessment, patients were assessed for study eligibility and classified as having severe or non-severe asthma. Data collected in SAWD included demographic characteristics; asthma, allergy and general medical history; medication use and adherence; asthma control; severe exacerbations; spirometry; biomarkers; and patient-reported measures related to health status and asthma-related quality of life. Further details are contained in the journal Online Supplement and SAWD protocol (http://www.severeasthma.org.au/tools-resources/toolkits/).

Current employment and productivity were assessed via the Work Productivity and Activity Impairment Questionnaire: General Health V2.0 (WPAI:GH).[20] Absenteeism was calculated as a percentage of the number of hours of work missed due to health reasons divided by usual work hours. Presenteeism and impairment in daily activities were calculated using Likert scale responses regarding self-rated impairment due to health reasons at work and in activities outside work, multiplied by 10 to scale between 0 and 100 (higher scores indicate greater impairment).

Statistical analysis

We computed descriptive characteristics of participants at baseline, comparing severe with non-severe asthma using Chi-square, Fisher's exact test, t-test and Wilcoxon rank-sum as appropriate. We examined whether asthma severity indicators were associated with being employed (in participants of working age; <65 years), absenteeism and presenteeism (in participants currently employed) and impairment in daily activity (in all participants) across repeated assessments. We used logistic or Gaussian generalised estimating equations (GEE), controlling for age, sex and assessment timepoint, modelling impairment as (1) a binary outcome (no reported problems versus some problems; referred to as "reported impairment") and (2) a continuous outcome when values were greater than 0 (referred to as "level or degree of impairment"). We also examined whether severe exacerbations in the year before baseline were associated with baseline productivity indicators using logistic and linear regression. We tested whether the association between impairment and asthma severity differed over time by adding an interaction term between assessment timepoint and severity indicators. Finally, we examined the association between asthma-related characteristics and presenteeism at baseline in the severe asthma group via binary logistic or linear regression, controlling for age and gender. Analyses were completed in Stata IC/15 (StataCorp LLC, USA) and the "gee" package[21] in R statistical language (R Foundation, Austria).[22] Statistical significance was considered at $p < 0.05$.

Results

Baseline characteristics

SAWD comprised 536 participants, 434 (81%) with severe asthma and 102 (19%) with non-severe asthma. Follow-up data were available in SAWD for 334 participants at 6 months, 254 at 12 months, 161 at 18 months, and 109 at 24 months (70.8%, 66.5%, 55.5% and 47.8% of the sample due for assessment at April 2017, respectively). There were four known deaths and 12 study withdrawals. Participants who had follow-up data recorded, compared with those who did not, were more likely to have severe asthma and were slightly older at baseline, but did not significantly differ in other key characteristics including workplace characteristics and asthma control (Online Supplement Table S2).

At baseline, the mean age of participants was 55.0 years (SD = 15.3) and 59% were female. Participants with severe and non-severe asthma were similar in age, gender, race, and atopic and smoking status, although those with severe asthma had poorer health status according to several indicators (Table 1). As expected, participants with severe asthma had poorer lung function, poorer asthma control, more past-year exacerbations and were prescribed a higher dose of ICS than participants with non-severe asthma, although they reported a similar asthma duration (mean±SD duration for overall sample 31.0±19.1 years). Participants with severe asthma were highly symptomatic, with median ACQ6 score of 2.0 (IQR 1.2-2.8). There was little change in asthma control over time (Figure 1).

Participants with severe asthma were using a median of four maintenance respiratory medications (IQR 3-5), compared with two medications in the non-severe group (IQR 2-3, $p < 0.001$). All participants were using ICS at baseline. Use of ICS/LABA combination inhalers was common in the overall sample (91.8%) and more common in participants with severe asthma (93.3% versus 85.3% in non-severe asthma, $p = 0.014$). In the severe asthma group, 24.4% were using maintenance oral corticosteroids and 19.1% were receiving omalizumab, whereas no participants with non-severe asthma used these medications.

Workplace productivity at baseline

Among participants of working age (<65 years; $N = 355$), 221 (62.3%) were employed at baseline, with little difference in the overall employment rate between severe and non-severe asthma (61.4% vs 66.2%, $p = 0.571$, Figure 2A). Discrepancies in employment rates between severe and non-severe asthma were apparent at younger ages (Figure 3). All participants with non-severe asthma between 30 and 50 years were employed ($N = 19$), whereas only 69% with severe asthma were employed (employed $N = 70$; not employed $N = 31$).

In the total sample, 243 participants (48.5%) were employed at baseline; 24.9% of workers reported some absenteeism and a majority of workers reported presenteeism in the past week (66.7%). At baseline, participants with severe asthma reported much higher presenteeism ($p < 0.001$) and activity impairment ($p = 0.002$) than those with non-severe asthma, but no significant difference in absenteeism (Figure 2A and 2B). In the severe asthma group, the rate of presenteeism was high, regardless of whether the participant had comorbid nasal polyps, rhinitis or allergic sensitisation (all $p > 0.05$, Figure 2C).

At baseline, presenteeism and activity impairment were strongly correlated ($\rho = 0.70$, $p < 0.001$), whereas absenteeism was less strongly correlated with presenteeism ($\rho = 0.39$, $p < 0.001$) and activity impairment ($\rho = 0.32$, $p < 0.001$). Absenteeism and presenteeism did not differ across sites (for sites with > 20 participants and after controlling for proportion of severe participants). However, employment rates significantly differed across sites, ranging from 34.6% to 78.8% (X^2 (9) = 28.4, $p = 0.001$).

Asthma severity, workplace productivity and activity limitations

Across all assessments, participants with severe asthma were 3.2 times more likely to report presenteeism ($p < 0.001$) and 2.3 times more likely to report impairment in daily activity ($p < 0.001$) compared to participants with non-severe asthma, adjusting for age, gender and assessment timepoint (Figure 4A; Online Supplement Table S3). Compared with non-severe asthma, participants with severe asthma who reported productivity impairment did not have a greater degree of presenteeism, although they had a greater degree of activity impairment. Participants with severe asthma were not more likely to report absenteeism.

Poorer asthma control according to the ACQ6 was associated with greater likelihood of reporting absenteeism, presenteeism and impairment in daily activity, as well as a greater degree of impairment when the impairment was reported (Figure 4C; Table S3). Excluding participants with non-severe asthma from this analysis did not change the observed effects. Higher pre-bronchodilator FEV_1% was also associated with lower likelihood of presenteeism and activity impairment and higher likelihood of being employed (Figure 4B; Table S3).

More exacerbations (either OCS courses, hospitalisations, or emergency department visits) in the year before baseline were associated with lower likelihood of being employed and greater likelihood of presenteeism and impairment in daily activity, as well as a greater degree of activity impairment, at baseline (Figure 4D; Table S3). Use of maintenance oral corticosteroids was not associated with any of the workplace productivity indicators or activity impairment ($p > 0.05$).

Change in workplace productivity over time

The proportion of participants employed remained stable over time (not shown) as did the level of presenteeism reported, particularly among participants with severe asthma (Figure 2D). Overall, there was little evidence that the association between asthma severity and

workplace productivity or activity impairment differed over the assessments (interaction $p > 0.05$). However, there was a significant interaction between assessment timepoint and ACQ6 in predicting presenteeism (interaction $p = 0.011$). Figure 5 shows that participants with the highest scores on ACQ6 reported increasing levels of presenteeism at later assessments, suggesting that patients with the worst asthma control and highest symptom burden were increasingly affected at work over time.

Predictors of presenteeism in people with severe asthma at baseline

In people with severe asthma at baseline, among a range of possible predictors, poorer asthma control scores, lower FEV_1%, more past-year exacerbations, poorer asthma quality of life, and symptoms of depression or anxiety were significantly associated with increased odds of reporting presenteeism, after controlling for age and gender (Figure 6; Table S4). Symptoms of depression or anxiety and asthma control were independently associated with reporting presenteeism when simultaneously entered into regression analyses (OR [95%CI]: depressive symptoms 1.16 [1.01-1.33], $p = 0.031$ and ACQ6 2.14 [1.39-3.31], $p = 0.001$; anxiety symptoms 1.11 [1.01-1.22], $p = 0.025$ and ACQ6 2.28 [1.48-3.49], $p < 0.001$, controlling for age and gender). Poorer asthma control and asthma quality of life, and, to a lesser extent, lower BMI were associated with a greater degree of presenteeism (Table S4). Medication use and immunological indicators (atopy, IgE, blood eosinophils) were not significantly associated with presenteeism (Figure 6; Table S4).

Discussion

Patients with severe asthma reported presenteeism and impairment in daily activity, but not absenteeism, more often than patients with non-severe asthma. Poorer asthma control was associated with a greater degree of absenteeism, presenteeism and impairment in daily activity, as well as worsening presenteeism over time. For each additional exacerbation per year, there was a 25% increase in reporting presenteeism. In people with severe asthma, presenteeism was associated with poorer asthma control, poorer asthma-related quality of life, and symptoms of depression or anxiety. These findings emphasise the importance of optimising asthma control, health status and mental health to promote participation of individuals with severe asthma in the workforce.

A key finding in this study was the high prevalence of presenteeism in asthma, which was significantly higher in severe asthma. The difference in presenteeism between severe and non-severe asthma was more prominent than impairment in non-work roles. Presenteeism, or "pushing through" at work to keep up with others, has been identified as a problem by severe asthma interviewees.[3] The severe asthma registry from China reported similar rates of employment and higher levels of presenteeism in patients with uncontrolled compared with controlled asthma (85.2% vs. 47.5% presenteeism, respectively).[23] Comparable findings have been observed in severe asthma clinics,[24] outpatient clinics[25] and from population-based representative random samples, although these studies typically include few participants on high-dose medication.[14,26–29] Studies assessing asthma-specific impairment, rather than general health impairment, also show that those with severe or uncontrolled asthma show greater impairment than controlled asthma.[30,31] However, using an asthma-specific version of the workplace productivity questionnaire may underestimate the true effect of severe asthma on workplace productivity, given physical and mental health comorbidity is high in asthma and often contributes to symptoms.

Previous studies from severe asthma registries have generally only reported on unemployment indicators of workplace productivity, where 15-26% of patients with severe asthma are not working due to asthma.[8,9,32,33] Our study suggests that younger age groups may be most adversely affected. It also highlights exacerbations and lung function as predictors of current employment status. Unlike other registries, although absenteeism in the previous week was relatively frequently reported in SAWD (25% of overall sample), there was little difference between severe and non-severe asthma. In part, this may be because participants who were exacerbating at baseline were excluded from SAWD until they were stable and the recruitment of non-severe patients from hospital-based respiratory clinics who may have had more disease-related impairment. However, we did observe that a one-point increase in ACQ6 almost doubled the chance of reporting absenteeism. Previous studies comparing absenteeism in severe or uncontrolled asthma with controlled asthma over periods longer than a week report even higher prevalence of absenteeism (36-43%) in severe patients than our study.[34–38] Cost analyses show that differences in indirect costs to the economy due to lost workdays between uncontrolled and controlled asthma are striking (€466.86 versus €44.60/month, based on the ACT).[25] Taken together, substantial levels of absenteeism and work deficits show that there is an urgent need to achieve asthma control and reduce exacerbations in severe asthma to improve workplace participation.

Another important finding from this study is that productivity impairments changed little over time and differences between severe and non-severe asthma were maintained. There was also evidence that patients with the worst asthma control have greater presenteeism over time. Other longitudinal studies in severe asthma have similarly observed stable or worsening workplace impairment over time in severe asthma.[39–41] These findings demonstrate the increased burden of severe asthma, and that effects of severe asthma on workplace productivity are enduring.

Determinants of presenteeism and other indicators of workplace impairment, beyond asthma control, have seldom been examined, indicating this as an area for further investigation. We identified poorer asthma control, poorer asthma-related quality of life, and more depression and anxiety symptoms as characteristics associated with presenteeism in severe asthma. The findings for depression and anxiety are novel, yet are not unexpected, given studies in non-asthma populations.[42,43] Effects of depression and anxiety on productivity may be even more profound than asthma control,[44] highlighting the importance of improving mental health in severe asthma. We identified few other predictors of presenteeism among a range of demographic, asthma and health status characteristics. Concordant with the current study, previous studies indicate that atopy and eosinophil levels are not associated with absenteeism.[6,45] While patients on multiple asthma medications have greater work and activity impairment,[27,46] effective new treatments, including biological agents, have been shown to reduce workplace impairment.[38,41,47]

We identified several limitations of this study. As SAWD is an observational registry, data are subject to selection bias, other unknown bias and confounding, and effects over time are not controlled. However, the strength of registry data is the generalisability of the findings due to the heterogeneity of the population. Registry data is an important complement to randomised controlled trial data, providing practice-based evidence. This study also used a convenience rather than random sample, so the representativeness of this sample of severe and non-severe asthma in general is not clear. Nevertheless, the sample characteristics are consistent with other registry samples although prevalence of atopy is higher in SAWD.[8,9,48] There were limitations in the measurement of workplace productivity. This study examined self-reported impairment over seven days, which, although positive in terms of the reliability of the estimate, may underestimate longer-term effects. Extended follow-up, including real-time sampling of workplace productivity, and verification with objective

indicators of workplace performance would be a novel improvement to assessing workplace productivity in severe asthma. It would be particularly useful for verifying the impact of mental health problems on presenteeism in severe asthma, independent of possible biased self-reporting due to negative self-evaluation. Data regarding the effects of asthma on probability of early retirement or employment choices would also be informative. SAWD did not collect information on type of employment, socioeconomic status, education, retirement age or whether participants access disability pensions, which further data collection could address. Finally, some data were incomplete, patients were lost to follow-up and follow-up assessments were yet to be completed at the time data were extracted from SAWD. However, baseline differences between participants who did and did not contribute follow-up data were minimal.

Workplace productivity loss is common in people with severe asthma, which may have significant consequences for their physical, financial, social and emotional wellbeing. Work impairment in severe asthma is associated with greater healthcare utilisation and more exacerbations over time.[6,30] Beyond presenteeism and absenteeism, people with severe asthma work less, switch jobs, are prevented from entering some professions, take disability leave and retire early, all of which may pose significant risks to their financial stability.[3,7–9,30,33,49] They report lower earnings compared with controlled asthma.[28,29,35,37] People with severe asthma worry about their work and non-work activity limitations and their finances, reporting fear that health costs will be unmanageable due to restrictions on their ability to work.[3] They report workplace discrimination and stigma due to asthma[7] and experience negative emotions of giving up work.[50] An adverse cycle may ensue whereby workplace impairment due to asthma symptoms and exacerbation generates stress that leads to further impairment, even when asthma symptoms resolve.

People with severe compared with non-severe asthma have a high symptom and disease burden, which significantly contributes to impairment at work and during other activities. We show that people with severe asthma, particularly those with poorer asthma control, are more likely to experience impairment at work. Patients in this registry, and others, are comprehensively monitored and optimally treated, however symptom control remained suboptimal. There is an urgent need for improvement in asthma control to safeguard against losses to financial and psychological wellbeing from work impairment. Although expensive, novel asthma therapies that improve asthma control and quality of life may have benefits to

an individual's productivity and the broader economy. Concentrating only on absenteeism as a measure of workplace impairment may miss the important issue of presenteeism: working while unwell at suboptimal capacity. Absenteeism and presenteeism may be key metrics for assessing intervention efficacy among people with severe asthma of working age.

Conflict of interest statement

SA Hiles' salary was funded by a grant from GlaxoSmithKline during the conduct of the study. **VM McDonald** has received speaker fees for unrelated work, grants for organising education unrelated work, and research funds for unrelated work from AstraZeneca, Menarini and GlaxoSmithKline. **M Peters** reports personal fees from GlaxoSmithKline for CME lectures and advisory board participation, personal fees from AstraZeneca, for CME lectures and personal fees from Novartis for advisory board participation outside the submitted work. **PN Reynolds** reports grants from TSANZ during the conduct of the study. **JW Upham** reports personal fees from Novartis, GlaxoSmithKline, AstraZeneca and TEVA outside the submitted work. **J Bowden** reports personal fees from AstraZeneca and GlaxoSmithKline during the conduct of the study. **LP Chung** reports fees for presentation and attendance at board meetings from AstraZeneca, GlaxoSmithKline, Menarini and Boehringer Ingelheim for work unrelated to the current manuscript. **M Hew** has undertaken contracted research for AstraZeneca, Sanofi, Novartis and GlaxoSmithKline; delivered education talks for GlaxoSmithKline, AstraZeneca and Novartis; participated on advisory boards/consultancies for AstraZeneca, GlaxoSmithKline and Seqirus; for all of which his employer (Alfred Health) has been reimbursed. **C Jenkins** reports personal fees from Novartis, AstraZeneca and Boehringer Ingelheim, and grants and personal fees from GlaxoSmithKline, outside the submitted work. **V Kritikos** reports other support from AstraZeneca outside the submitted work. **N Radhakrishna** has received speaker fees from Mundipharma, Boehringer Ingelheim and AstraZeneca. **H Reddel** reports grants, personal fees and non-financial support from AstraZeneca; grants, personal fees and non-financial support from GlaxoSmithKline; personal fees from Merck; personal fees from Novartis; personal fees from Teva; personal fees from Mundipharma; personal fees from Boehringer Ingelheim outside the submitted work. **J Rimmer** reports unrelated honoraria form GlaxoSmithKline, Stallergenes, Seqirus and AstraZeneca. **M Sutherland** reports personal fees from AstraZeneca outside the submitted work. **PG Gibson** has received research grants and speaker fees from AstraZeneca, GlaxoSmithKline and Novartis. All other co-authors declare no conflict of interest.

Acknowledgments

This study was funded through grants from AstraZeneca, GlaxoSmithKline, Novartis, Boehringer Ingelheim and Roche. We thank the Thoracic Society of Australia and New Zealand for providing governance and the Woolcock Institute of Medical Research and the Hunter Medical Research Institute. We thank the study participants and members of the Australasian Severe Asthma Network, including SAWD site investigators, clinical research staff, staff involved in data entry staff and personnel involved in statistical and information technology support throughout the project.

References

1. O'Neill S, Sweeney J, Patterson CC, et al. The cost of treating severe refractory asthma in the UK: An economic analysis from the British Thoracic Society Difficult Asthma Registry. *Thorax* 2015;70:376-378.

2. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;43:343-373.

3. Foster JM, McDonald VM, Guo M, et al. "I have lost in every facet of my life": The hidden burden of severe asthma. *Eur Respir J* 2017;50:1700765.

4. Bergström G, Bodin L, Hagberg J, et al. Sickness presenteeism today, sickness absenteeism tomorrow? A prospective study on sickness presenteeism and future sickness absenteeism. *J Occup Environ Med* 2009;51:629-638.

5. Mancuso CA, Rincon M, Charlson ME. Adverse work outcomes and events attributed to asthma. *Am J Ind Med* 2003;44:236-245.

6. Eisner MD, Yelin EH, Katz PP, et al. Risk factors for work disability in severe adult asthma. *Am J Med* 2006;119:884-891.

7. McClellan VE, Garrett JE. Asthma and the employment experience. *N Z Med J* 1990;103:399-401. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2143568.

8. Heaney LG, Brightling CE, Menzies-Gow A, et al. Refractory asthma in the UK: Cross-sectional findings from a UK multicentre registry. *Thorax* 2010;65:787-94.

9. Schleich F, Brusselle G, Louis R, et al. Heterogeneity of phenotypes in severe asthmatics. The Belgian Severe Asthma Registry (BSAR). *Respir Med* 2014;108:1723-1732.

10. Johns G. Presenteeism in the workplace: A review and research agenda. *J Organ Behav* 2010;31:519-542.

11. Hemp P. Presenteeism: At work - But out of it. *Harv Bus Rev* 2004;82:49-58.

12. Vänni K, Neupane S, Nygård CH. An effort to assess the relation between productivity loss costs and presenteeism at work. *Int J Occup Saf Ergon* 2017;23:33-43.

13. Schultz AB, Chen C-Y, Edington DW. The cost and impact of health conditions on presenteeism to employers: A review of the literature. *Pharmacoeconomics* 2009;27:365-78.

14. Sadatsafavi M, Rousseau R, Chen W, et al. The preventable burden of productivity loss due to suboptimal asthma control: A population -based study. *Chest* 2014;145:787-793.

15. Harris PA, Taylor R, Thielke R, et al. Research Electronic Data Capture (REDCap) - A metadata driven methodology and workflow process for providing translational research informatict support. *J Biomed Inform* 2009;42:377-381.

16. Tay TR, Lee J, Radhakrishna N, et al. A structured approach to specialist-referred difficult asthma patients improves control of comorbidities and enhances asthma outcomes. *J Allergy Clin Immunol Pract* 2017;5:956-964.e3.

17. Global Initiative for Asthma. *Global Strategy for Asthma Management and Prevention*.; 2014. Available at: www.ginathma.org.

18. Juniper EF, Svensson K, Mörk AC, et al. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med* 2005;99:553-558.

19. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the Asthma Control Test: A survey for assessing asthma control. *J Allergy Clin Immunol* 2004;113:59-65.

20. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993;4:353-65.

21. Carey VJ, Ported to R by Thomas Lumley (versions 3.13 and 4.4) and Brian Ripley (version 4.13). gee: Generalized esimation equation solver (R package version 4.13-19). 2015. Available at: http://cran.r-project.org/package=gee.

22. R Core Team. *R: A language and environment for statistical computing*. Vienna, Austria:

R Foundation for Statistical Computing; 2017. Available at: https://www.r-project.org/.

23. Wang G, Wang F, Gibson PG, et al. Severe and uncontrolled asthma in China: A cross-sectional survey from the Australasian Severe Asthma Network. *J Thorac Dis* 2017;9:1333-1344.

24. Beharry S, Gidla D, Maharaj A, et al. Reality and understanding of asthma control. *Chron Respir Dis* 2015;12:340-346.

25. Ojeda P, de Burgoa VS. Costs associated with workdays lost and utilization of health care resources because of asthma in daily clinical practice in Spain. *J Investig Allergol Clin Immunol* 2013;23:234-241.

26. Ding B, DiBonaventura M, Karlsson N, et al. Asthma-chronic obstructive pulmonary disease overlap syndrome in the urban Chinese population: Prevalence and disease burden using the 2010, 2012, and 2013 China National Health and Wellness Surveys. *Int J Chron Obstruct Pulmon Dis* 2016;11:1139-1150.

27. Sullivan PW, Slejko JF, Ghushchyan VH, et al. The relationship between asthma, asthma control and economic outcomes in the United States. *J Asthma* 2014;51:769-778.

28. Vietri J, Burslem K, Su J. Poor asthma control among US workers. *J Occup Environ Med* 2014;56:425-430.

29. Williams SA, Wagner S, Kannan H, et al. The association between asthma control and health care utilization, work productivity loss and health-related quality of life. *J Occup Environ Med* 2009;51:780-785.

30. Chen H, Blanc PD, Hayden ML, et al. Assessing productivity loss and activity impairment in severe or difficult-to-treat asthma. *Value Heal* 2008;11:231-239.

31. Wertz DA, Pollack M, Rodgers K, et al. Impact of asthma control on sleep, attendance at work, normal activities, and disease burden. *Ann Allergy, Asthma Immunol* 2010;105:118-123.

32. Sweeney J, Patterson CC, Menzies-Gow A, et al. Comorbidity in severe asthma requiring systemic corticosteroid therapy: Cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. *Thorax* 2016;71:339-

346.

33. Gaga M, Papageorgiou N, Yiourgioti G, et al. Risk factors and characteristics associated with severe and difficult to treat asthma phenotype: An analysis of the ENFUMOSA group of patients based on the ECRHS questionnaire. *Clin Exp Allergy* 2005;35:954-959.

34. Colice G, Wu EQ, Birnbaum H, et al. Healthcare and workloss costs associated with patients with persistent asthma in a privately insured population. *J Occup Environ Med* 2006;48:794-802.

35. Costa E, Bregman M, Araujo D V, et al. Asthma and the socio-economic reality in Brazil. *World Allergy Organ J* 2013;6:20.

36. Dean BB, Calimlim BM, Kindermann SL, et al. The impact of uncontrolled asthma on absenteeism and health-related quality of life. *J Asthma* 2009;46:861-866.

37. Peters SP, Jones CA, Haselkorn T, et al. Real-world Evaluation of Asthma Control and Treatment (REACT): Findings from a national web-based survey. *J Allergy Clin Immunol* 2007;119:1454-1461.

38. Gonzalez Barcala FJ, La Fuente-Cid RD, Alvarez-Gil R, et al. Factors associated with a higher prevalence of work disability among asthmatic patients. *J Asthma* 2011;48:194-199.

39. Sullivan SD, Rasouliyan L, Russo PA, et al. Extent, patterns, and burden of uncontrolled disease in severe or difficult-to-treat asthma. *Allergy Eur J Allergy Clin Immunol* 2007;62:126-133.

40. Lindström I, Pallasaho P, Luukkonen R, et al. Reduced work ability in middle-aged men with asthma from youth- a 20-year follow-up. *Respir Med* 2011;105:950-955.

41. Zazzali JL, Raimundo KP, Trzaskoma B, et al. Changes in asthma control, work productivity, and impairment with omalizumab: 5-year EXCELS study results. *Allergy Asthma Proc* 2015;36:283-292.

42. Beck A, Crain L, Solberg L, et al. Does severity of depression predict magnitude of productivity loss? *Am J Manag Care* 2014;20:e294-e301.

43. Evers KE, Castle PH, Prochaska JO, et al. Examining relationships between multiple

health risk behaviors, well-being, and productivity. *Psychol Rep* 2014;114:843-853.

44. Moullec G, Fitzgerald JM, Rousseau R, et al. Interaction effect of psychological distress and asthma control on productivity loss? *Eur Respir J* 2015;45:1557-1565. Available at: http://dx.doi.org/10.1183/09031936.00141614.

45. Zeiger RS, Schatz M, Dalal AA, et al. Blood eosinophil count and outcomes in severe uncontrolled asthma: A prospective study. *J Allergy Clin Immunol Pract* 2017;5:144-153.

46. Tan H, Sarawate C, Singer J, et al. Impact of asthma controller medications on clinical, economic, and patient-reported outcomes. *Mayo Clin Proc* 2009;84:675-684.

47. Mansur AH, Srivastava S, Mitchell V, et al. Longterm clinical outcomes of omalizumab therapy in severe allergic asthma: Study of efficacy and safety. *Respir Med* 2017;124:36-43.

48. Moore WC, Bleecker ER, Curran-Everett D, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol* 2007;119:405-413.

49. Yelin E, Katz P, Balmes J, et al. Work life of persons with asthma, rhinitis, and COPD: A study using a national, population-based sample. *J Occup Med Toxicol* 2006;1.

50. Foster J, Reddel H, Guo M, et al. *Severe asthma - uncovering the reality. A qualitative study of the lived experience of Australians with severe asthma*. Fortitude Valley, QLD, Australia; 2016.

Figure captions

Figure 1. Asthma Control Questionnaire (ACQ6; higher scores indicate less control) and Asthma Control Test (ACT; lower scores indicate less control) across assessments for participants with severe and non-severe asthma.

Figure 2. Workplace productivity in participants with severe and non-severe asthma. (A) Proportion of participants who reported being employed, absenteeism, presenteeism and impairment in daily activity at baseline; (B) Median levels of absenteeism, presenteeism and impairment in daily activity at baseline; (C) Proportion of participants with severe asthma

reporting presenteeism according to comorbidity of nasal polyps, rhinitis or allergic sensitisation at baseline; (D) Median levels of presenteeism across study assessments. ** $p < 0.01$; *** $p < 0.001$.

Figure 3. Percentage of participants employed across age groups.

Figure 4. Associations between asthma severity indicators and being employed or reporting impairments in productivity (versus no reported impairment). Analyses were generalised estimating equations with exchangeable correlation structure, controlling for sex, age and assessment timepoint and clustered by assessment timepoint. Data from all five assessments were used except for the exacerbations analyses where only baseline data were used. Confidence intervals were calculated from robust standard errors. Abbreviations: ACQ6: Asthma Control Questionnaire 6-item; CI: confidence interval; FEV_1%: forced expiratory volume in 1 second % predicted (10 unit change); OCS: oral corticosteroid; OR: odds ratio.

Figure 5. Interaction between Asthma Control Questionnaire (ACQ6) and assessment visit predicting workplace presenteeism, predicted from generalised linear model analysis. Participants with the highest values of ACQ6 (poorest asthma control) reported increasing levels of presenteeism across the five assessments (ACQ6*assessment interaction $p = 0.011$).

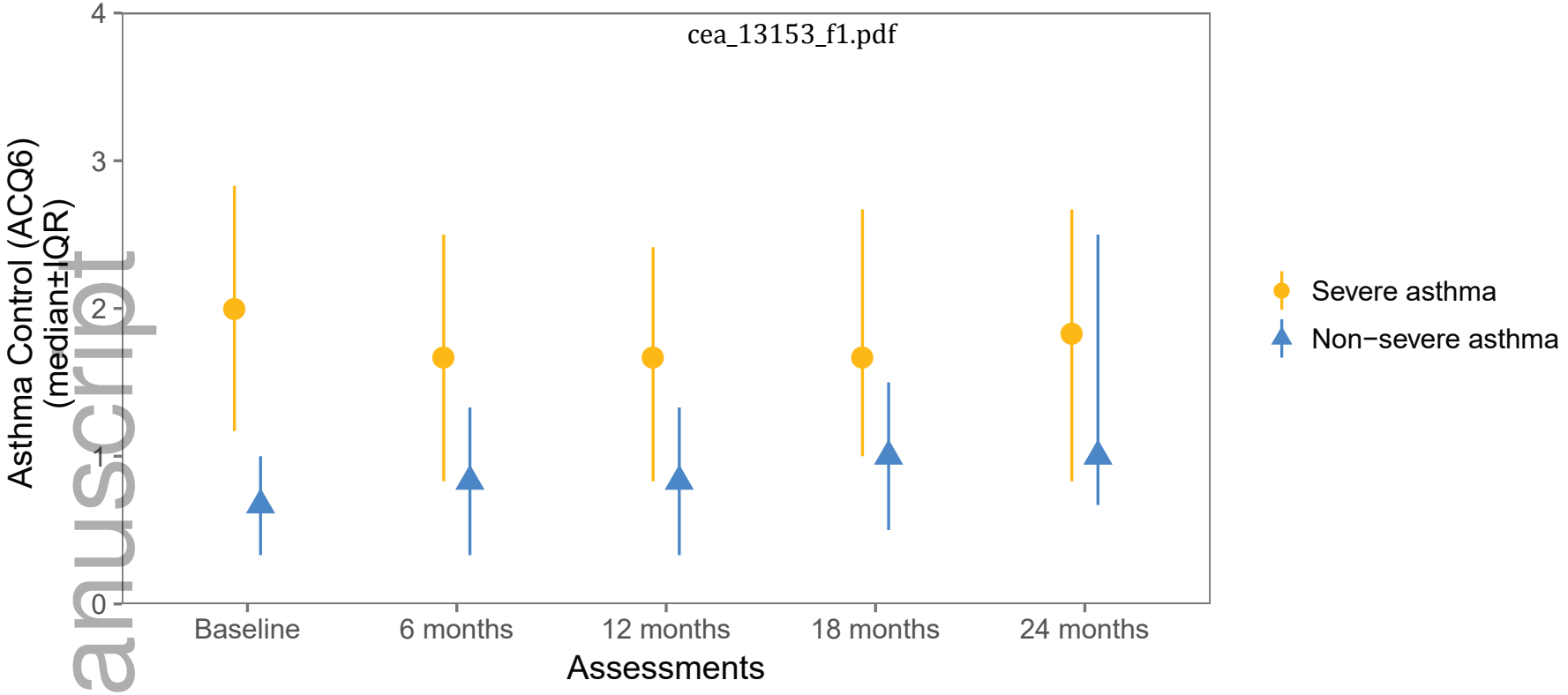
Figure 6. Associations between asthma severity characteristics, health status characteristics and immunological indicators at baseline. Abbreviations: CI: confidence interval; FEV_1%: forced expiratory volume in 1 second percent predicted (10 unit change); HADS: Hospital Anxiety and Depression Scale: N: number; OR: odds ratio.**Table 1.** Baseline demographic, clinical and quality of life characteristics according to severity group.

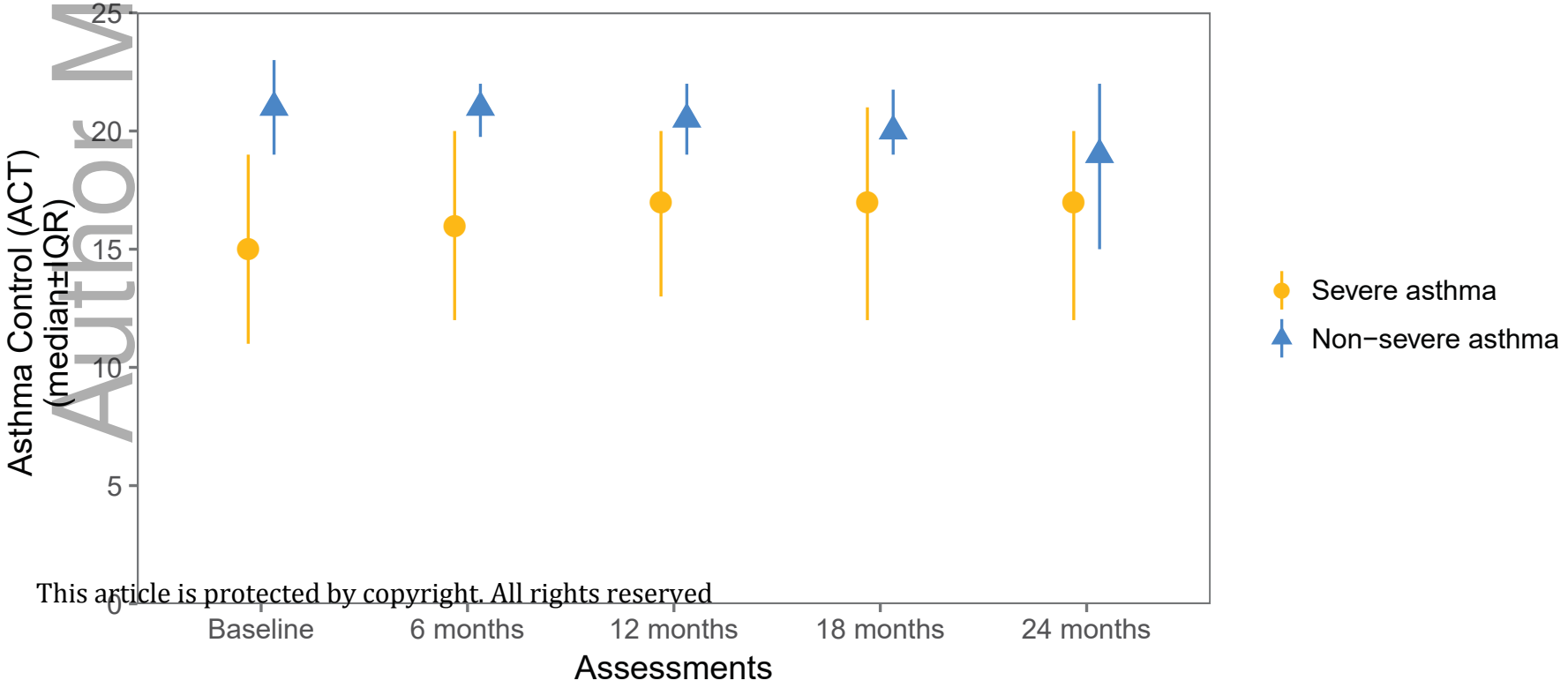
	Severe asthma N = 434		**Non-severe asthma N = 102**		***p***
Demographic characteristics					
Age (years), mean (SD)	54.8	(14.9)	56.0	(16.9)	.506
Gender, N (%)					
Female	260	(59.9)	56	(54.9)	
Male	174	(40.1)	46	(45.1)	.372
Race, N (%)					
White	290	(85.3)	76	(79.2)	

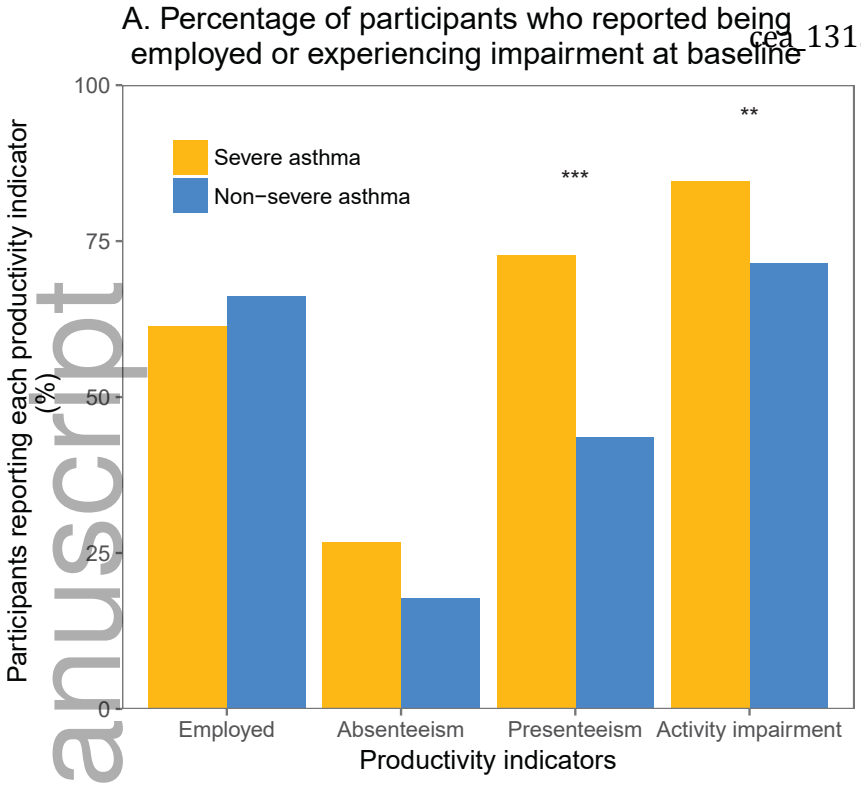
Asian	32	(9.4)	18	(18.8)	
Pacific islander	6	(1.8)	1	(1.0)	
Other	12	(3.5)	1	(1.0)	.060
Smoking status, N (%)					
Never smoked	267	(62.2)	66	(66.0)	
Ex-smoker	149	(34.7)	34	(34.0)	
Current smoker	13	(3.0)	0	(0)	.208
Pack years, median (IQR)	10.5	(2.4, 26.8)	5.9	(1.0, 13.8)	.018
BMI, median (IQR)	30.0	(25.9, 34.8)	27.4	(24.8, 30.3)	<.001
Number of comorbid conditions, median (IQR)	3.0	(2.0, 4.0)	2.0	(1.0, 3.0)	<.001
Asthma characteristics					
Asthma duration (years), mean (SD)	30.7	(19.0)	32.4	(19.4)	.419
ACQ6, median (IQR)	2.0	(1.2, 2.8)	0.7	(0.3, 1.0)	<.001
ACQ6 ≥ 2 (N, %)	229	(54.0)	0	(0)	<.001
ACT total score, median (IQR)	15.0	(11.0, 19.0)	21.0	(19.0, 23.0)	<.001
Pre-bronchodilator					
FEV_1 % predicted, mean (SD)	66.9	(21.2)	79.7	(19.4)	<.001
FVC % predicted, mean (SD)	81.5	(20.3)	88.7	(15.0)	<.001
FEV1/FVC % predicted, mean (SD)	0.82	(0.17)	0.91	(0.14)	<.001
Post-bronchodilator					
FEV_1 % predicted, mean (SD)	73.1	(21.9)	83.5	(19.3)	<.001
FVC % predicted, mean (SD)	85.7	(18.3)	90.4	(15.6)	.016
FEV_1/FVC % predicted, mean (SD)	0.66	(0.14)	0.72	(0.12)	<.001
ICS daily dose, µg beclomethasone equivalent units, median (IQR)	2000.0	(1600.0, 2000.0)	720.0	(400.0, 800.0)	<.001
Number of respiratory medications, median (IQR)	4.0	(3.0, 5.0)	2.0	(2.0, 3.0)	<.001
Severe exacerbations in the past year					
Number of OCS initiations, median (IQR)	2.0	(0.0, 4.0)	0.0	(0.0, 1.0)	<.001
Ever hospitalised, N (%)	96	(22.1)	2	(2.0)	<.001
Ever visited emergency department,	104	(24.0)	4	(3.9)	<.001

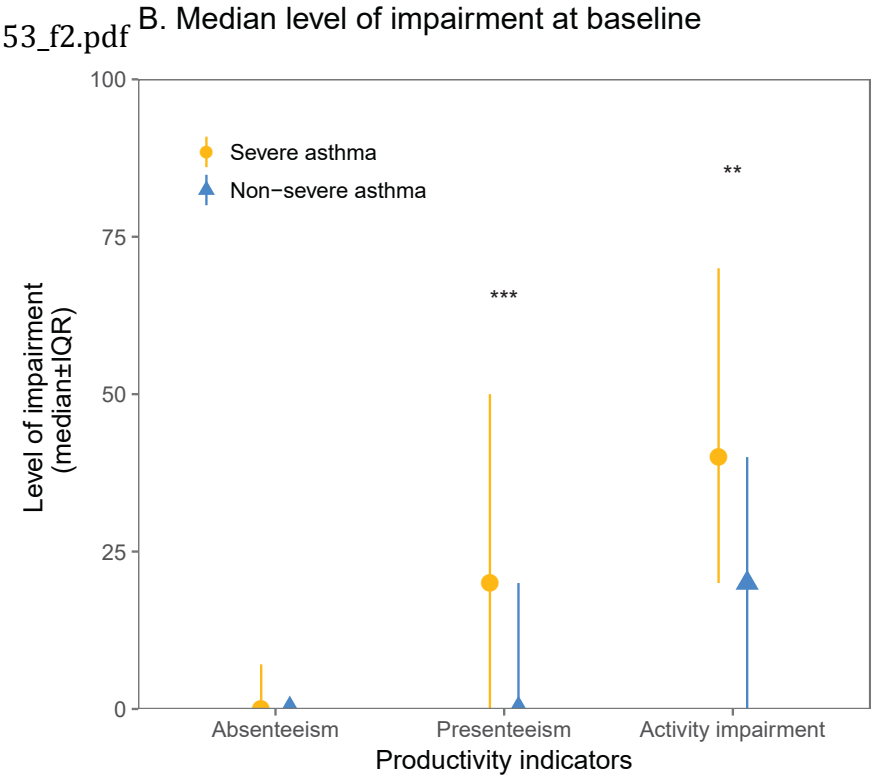
N (%)					
Atopy, N (%)	214	(79.6)	67	(81.7)	.753
IgE ≥ 30 kU/L, N (%)	278	(89.4)	19	(76.0)	.055
Blood eosinophils (10^9/L), median (IQR)	0.2	(0.1, 0.4)	0.3	(0.2, 0.4)	.576
Quality of life and mental health characteristics					
AQLQ, median (IQR)					
Activity	5.1	(3.9, 5.9)	6.5	(5.9, 6.7)	<.001
Symptoms	4.8	(3.6, 5.8)	6.1	(5.7, 6.6)	<.001
Emotions	5.0	(3.4, 6.2)	6.4	(5.8, 6.8)	<.001
Environment	5.2	(3.8, 6.2)	6.2	(5.5, 6.5)	<.001
Total	5.0	(3.8, 5.8)	6.2	(5.7, 6.6)	<.001
HADS anxiety score, median (IQR)	6.0	(3.0, 10.0)	5.0	(2.0, 8.0)	.033
HADS depression score, median (IQR)	4.0	(2.0, 7.0)	2.0	(1.0, 4.0)	<.001

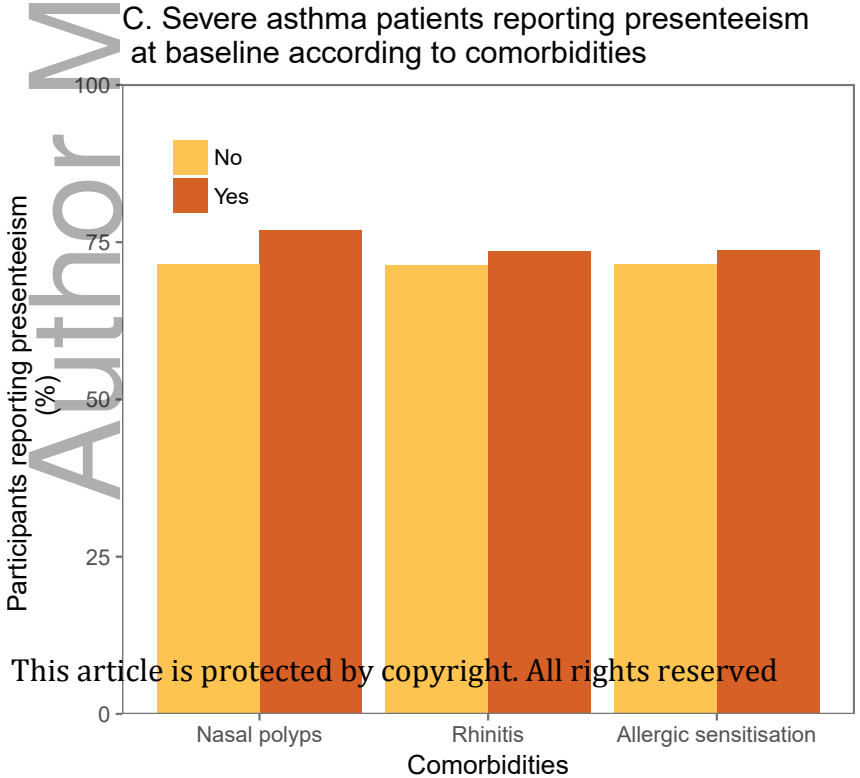
1 ACQ6: Asthma Control Questionnaire 6-item; ACT: Asthma Control Test; AQLQ: Asthma
2 Quality of Life Questionnaire; BMI: body mass index; FVC: forced vital capacity; FEV_1:
3 forced expiratory volume in 1 second; GINA: Global Initiative for Asthma; HADS: Hospital
4 Anxiety and Depression Scale; ICS: inhaled corticosteroids; OCS: oral corticosteroids.

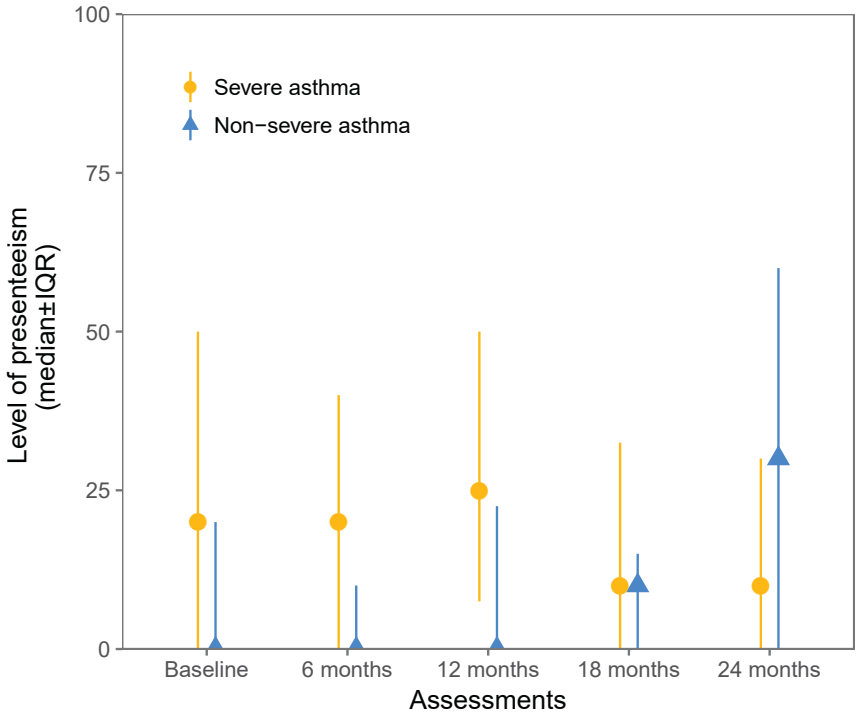


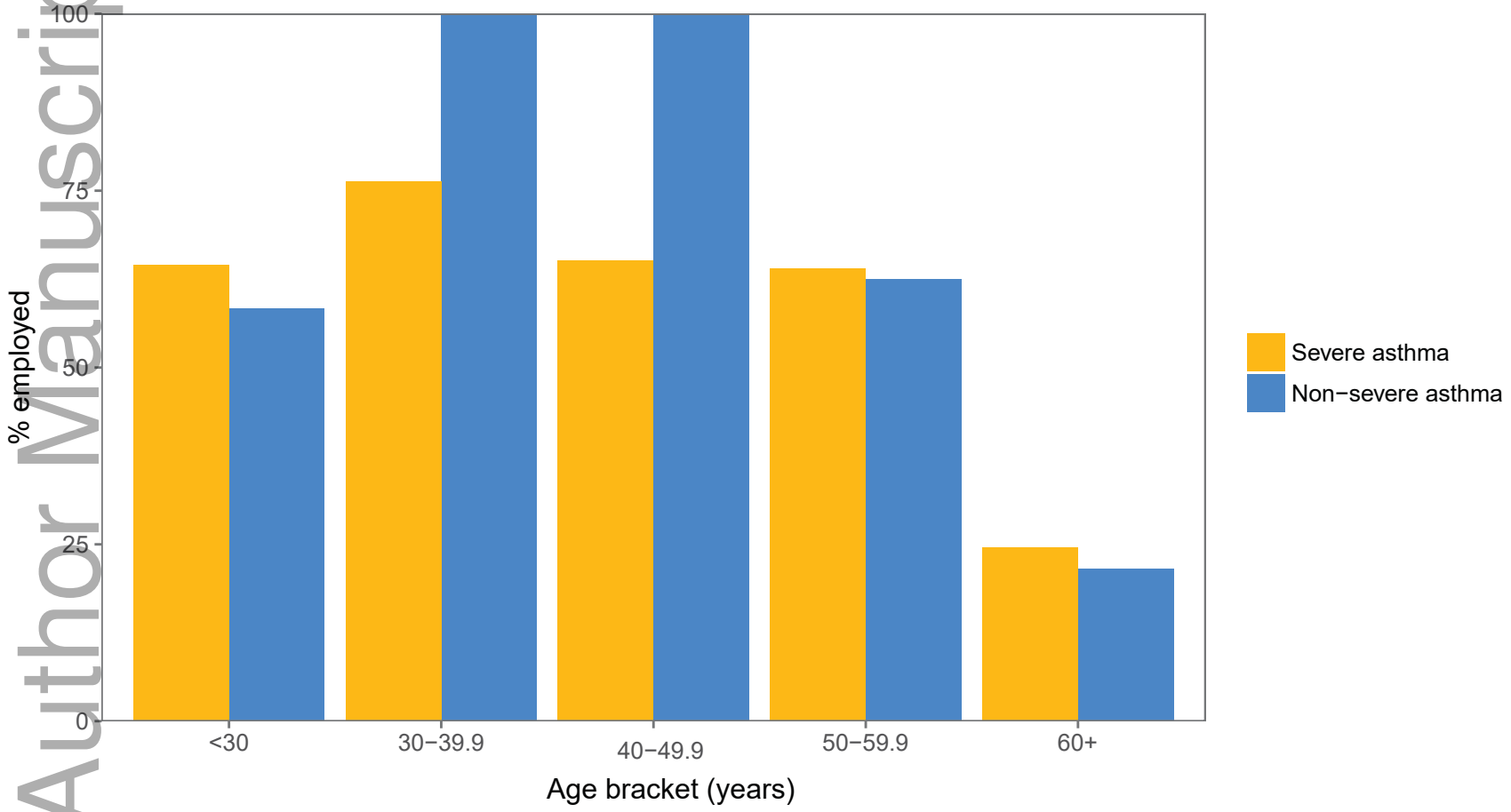


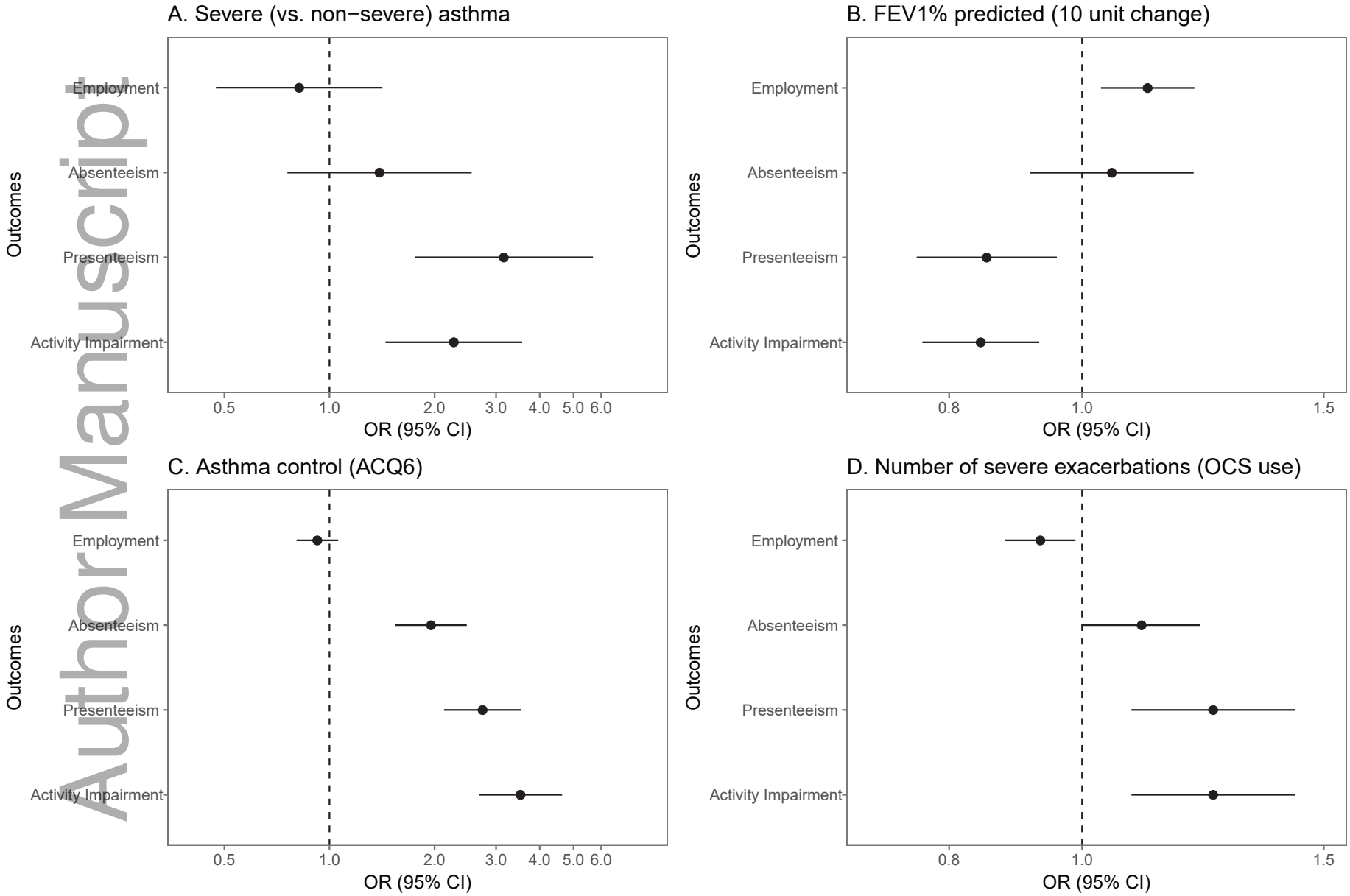


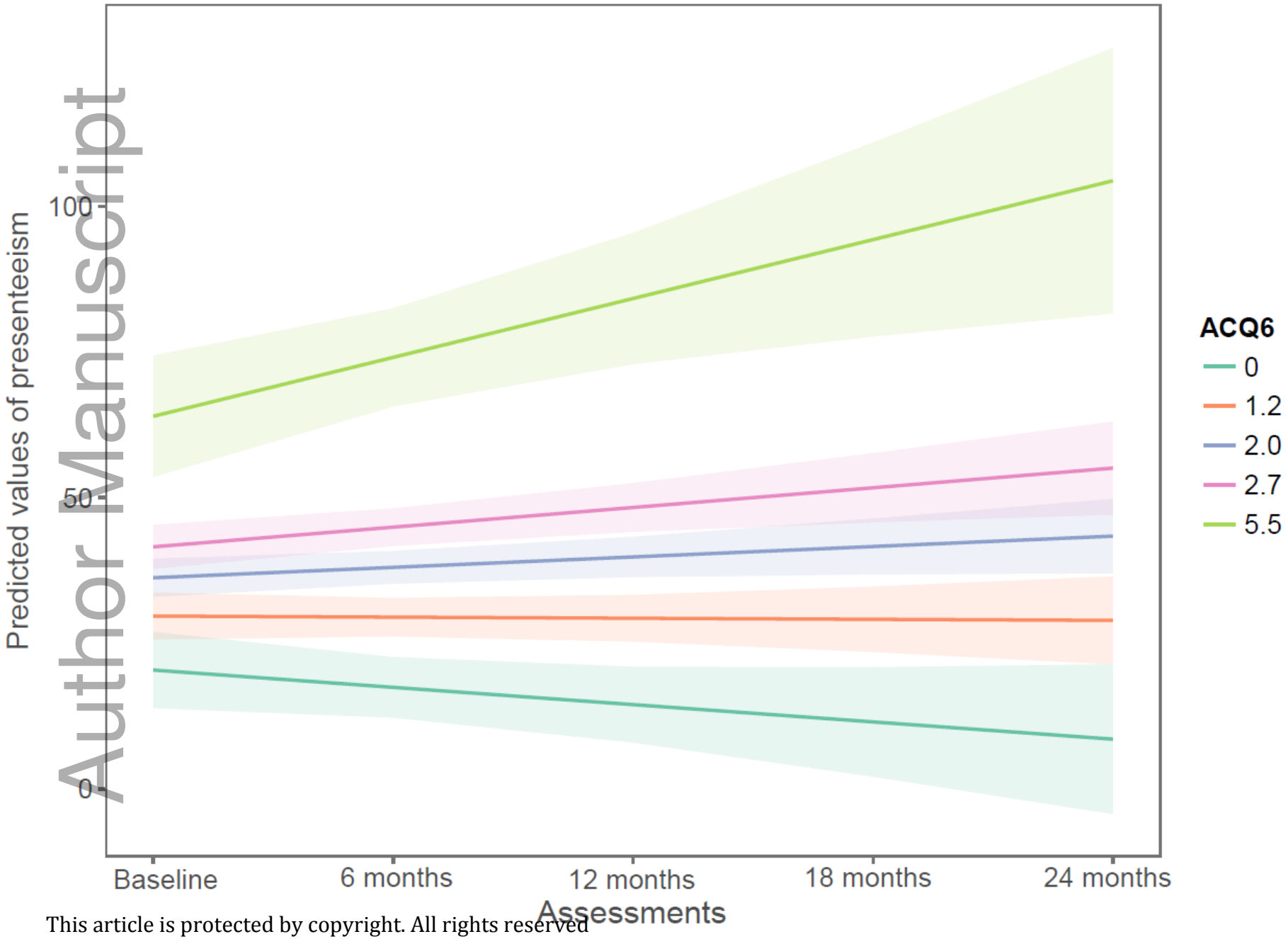


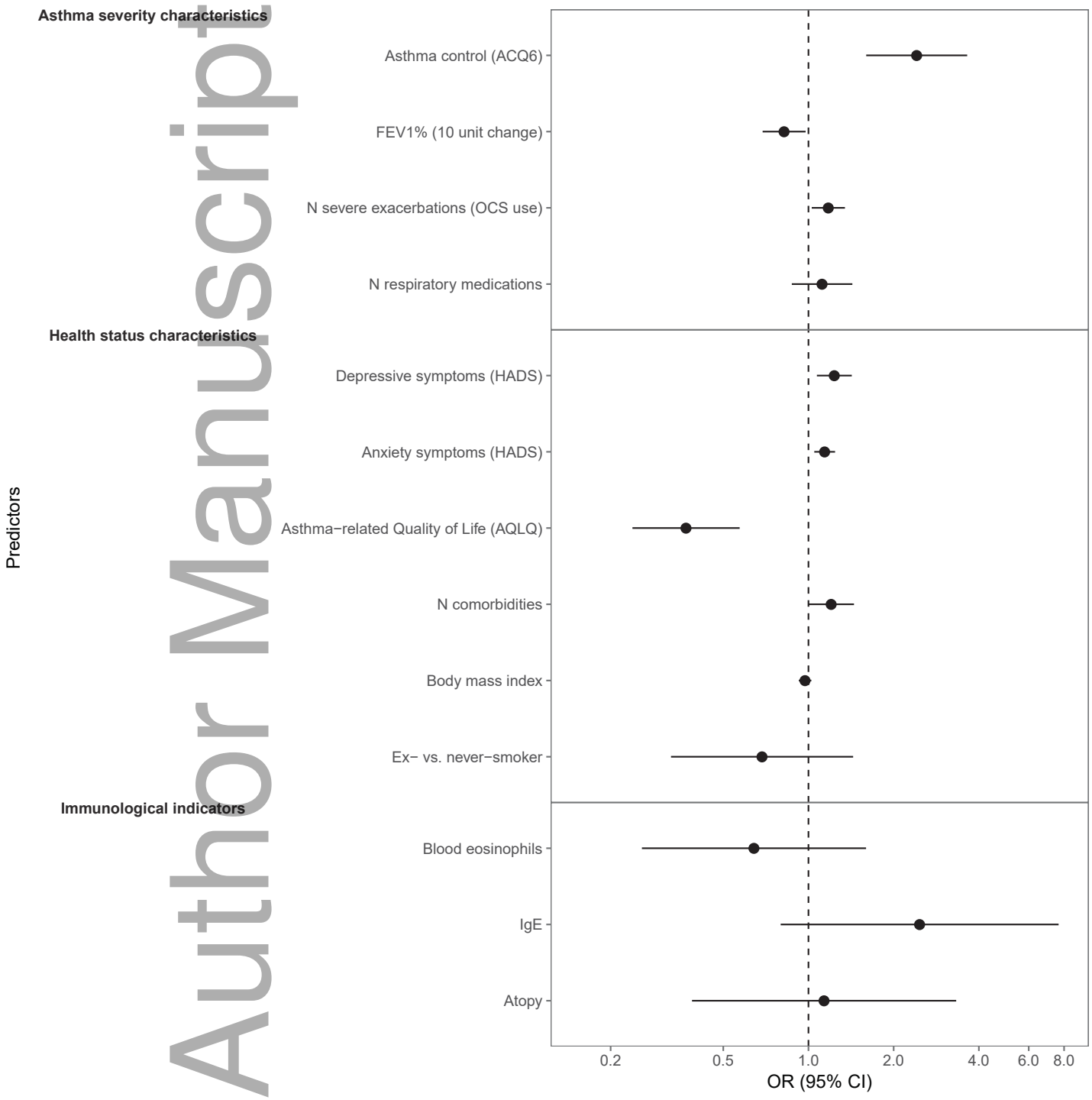












Author/s:
Hiles, SA;Harvey, ES;McDonald, VM;Peters, M;Bardin, P;Reynolds, PN;Upham, JW;Baraket, M;Bhikoo, Z;Bowden, J;Brockway, B;Chung, LP;Cochrane, B;Foxley, G;Garrett, J;Hew, M;Jayaram, L;Jenkins, C;Katelaris, C;Katsoulotos, G;Koh, MS;Kritikos, V;Lambert, M;Langton, D;Rivero, AL;Marks, GB;Middleton, PG;Nanguzgambo, A;Radhakrishna, N;Reddel, H;Rimmer, J;Southcott, AM;Sutherland, M;Thien, F;Wark, PAB;Yang, IA;Yap, E;Gibson, PG

Title:
Working while unwell: Workplace impairment in people with severe asthma

Date:
2018-06

Citation:
Hiles, S. A., Harvey, E. S., McDonald, V. M., Peters, M., Bardin, P., Reynolds, P. N., Upham, J. W., Baraket, M., Bhikoo, Z., Bowden, J., Brockway, B., Chung, L. P., Cochrane, B., Foxley, G., Garrett, J., Hew, M., Jayaram, L., Jenkins, C., Katelaris, C. ,... Gibson, P. G. (2018). Working while unwell: Workplace impairment in people with severe asthma. CLINICAL AND EXPERIMENTAL ALLERGY, 48 (6), pp.650-662. https://doi.org/10.1111/cea.13153.