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ORIGINAL RESEARCH

Management of People with Asthma in Primary Care by Smoking Status: A Cohort Study

Rutao Jia[1], Sarah Cook[2], Jennifer K Quint[1], Hannah Whittaker[1]

[1]School of Public Health, Imperial College London, London, UK; [2]Department of Health Services Research and Policy, Faculty of Public Health and Policy, London School of Hygiene & Tropical Medicine, London, UK

Correspondence: Hannah Whittaker, School of Public Health, Imperial College London, White City Campus, 84 Wood Lane, London, W12 0BZ, UK, Email h.whittaker@imperial.ac.uk

Background: Previous studies suggest that cigarette smokers with chronic respiratory disease may be managed differently. However, evidence is limited on whether smoking status impacts asthma management.

Methods: Data from the UK Clinical Practice Research Datalink (CPRD) Aurum were used to define a cohort of adults (aged over 18) diagnosed with asthma between January 1, 2010, and March 31, 2021. Start of follow-up was defined at first recorded asthma diagnosis. End of follow-up was March 31, 2021, or earlier if patients died or left the general practice. The exposure was the most recently recorded cigarette smoking status prior to asthma diagnosis, categorised as never, ex, or current smokers. Two outcome measures were used to assess asthma management: i) a record of at least one inhaled corticosteroid (ICS) prescription in the first year of follow-up and ii) asthma annual review visits over the follow-up period. Logistic and negative binomial regression models were applied, respectively, adjusting for potential confounders. An interaction with sex was tested to account for differences in asthma management in males and females.

Results: Among 241,624 adults with asthma (59.6% female, mean age 50.8), current smokers were less likely to receive ICS than never smokers (OR 0.94, 95% CI 0.91–0.96), while ex-smokers were more likely (OR 1.09, 95% CI 1.07–1.11). A sex interaction showed males were less likely to receive ICS than females among never smokers. Current smokers also had lower annual review rates (IRR 0.83, 95% CI 0.82–0.84), whereas ex-smokers had rates similar to never smokers (IRR 0.99, 95% CI 0.98–1.00). Males had lower review rates than females among never smokers only.

Conclusion: Cigarette smoking status influences asthma management. Findings highlight the importance of considering smoking status in planning and tailoring asthma care.

Keywords: asthma, smoking, management

Introduction

According to the Global Burden of Disease Study, tobacco is identified as the leading risk factor for the loss of disability-adjusted life years (DALYs) and there are over 112 million current smokers in Europe.[1,2] Smoking is not only a risk factor for respiratory diseases but also a behavior that carries significant social stigma.[3] Among these, stigma is strongly influenced by how individuals attribute responsibility for smoking and by fears of second-hand smoke, while smoking behavior itself is shaped by a complex mix of genetic, educational, and socioeconomic factors and is difficult to quit.[2,4,5] Interestingly, stigmatization of smoking does not necessarily lead to cessation.[5] On the contrary, it may limit smokers' access to healthcare, including delays in seeking medical treatment and differences in the availability and quality of medical services.[5]

Previous research has shown that people with lung cancer and chronic obstructive pulmonary disease (COPD) experience stigma due to smoking which can manifest internally through feelings such as shame, guilt, or self-blame, and externally, through judgment from others, including healthcare professionals.[6–8] Studies show that patients who smoke or have previously smoked report discomfort with disclosing this to healthcare professionals.[8]

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In terms of asthma, there is limited evidence as to whether smoking status influences asthma care. This is particularly important given that despite smoking cessation guidelines, around 50% of adults with asthma have a history of smoking, making it a potential risk factor.[9] Few studies have investigated how smoking status influences asthma care, and none have compared asthma management between smokers and non-smokers. Therefore, we aimed to investigate the relationship between smoking status and two key asthma management outcomes, prescribing inhaled corticosteroids (ICS) and asthma annual reviews, in people with asthma in the UK using electronic healthcare records.

Materials and Methods

Data Source

This cohort study utilized electronic healthcare data from CPRD Aurum (CPRD), comprising data from general practices (GP) across England. CPRD includes information on diagnoses, prescriptions, test results, symptoms, referrals, and lifestyle factors and is representative of the population of England in terms of age, sex, socioeconomic deprivation, and geographic spread.[10] Secondary care Hospital Episode Statistics (HES) and Index of Multiple Deprivation (IMD) data were linked to CPRD to define study covariates.

Study Population

We included individuals who met the following inclusion criteria: i) were aged over 18 with a primary care diagnosis of asthma, ii) were registered with a participating GP at least one year prior to asthma diagnosis, and iii) had data on smoking status prior to asthma diagnosis. The start of the follow-up was the date of the first recorded asthma diagnosis (Supplementary methods). The end of follow-up was earliest of death, end of GP registration, or March 31, 2021.

Exposure

The most recent recorded smoking status defined before the first asthma diagnosis, was identified from CPRD using "medcodeid" codes in CPRD. Individuals were classified as current smokers, ex-smokers, and never smokers. Individuals whose most recent smoking code was "never smoker" but who had a previous "current smoker" code were categorised as "ex-smokers" related to cigarette smoking. Please see the following Github link for all code lists used for this study, including codes and algorithms used for smoking status (https://github.com/NHLI-Respiratory-Epi/Smoking_ICS_AR).

Outcomes

The outcomes included: 1) at least one ICS-containing medication prescribed within one year of asthma diagnosis categorised as a binary variable (individuals who died or transferred out of their GP practice in the first year were excluded), and 2) asthma annual review visits defined as the number of reviews recorded per patient over the follow-up period. Information on ICS prescriptions and asthma annual review visits was obtained from CPRD and all ICS-containing medications, regardless of dose or duration were included.

Confounders

Primary care-related covariates included age, sex, body mass index (BMI) (defined as a continuous measure in kg/m^2), breathlessness, and comorbidities, including depression and anxiety. Confounders were chosen a priori based on the literature. Breathlessness, depression, and anxiety were coded as binary variables, defined as having a recorded diagnosis or symptom within 2 years of patients' asthma diagnosis date (vs never). In addition, IMD was derived from linked IMD data (defined as quintiles where IMD 1 represents the least deprived and 5 the most deprived) and ethnicity was defined using linked primary and secondary care data (defined as White, Black, South Asian, Mixed, and Other). Whilst blood eosinophils were not included as a confounder, these were included in the baseline table for descriptive purposes. These were defined as having a blood eosinophil count recorded within 2 years of the index date.

Statistical Analysis

Baseline characteristics were summarized by calculating mean ± SD (standard deviation) for continuous variables and numbers and percentages for categorical variables.

We used logistic regression to investigate the association between baseline smoking status and ICS prescriptions within one year of asthma diagnosis. Negative binomial regression was used to investigate the association between baseline smoking status and rates of asthma annual review visits over the whole follow-up. Both crude and fully adjusted models were performed, adjusting for age, sex, BMI, IMD, ethnicity, breathlessness, and comorbidities including depression and anxiety.

Given that smoking status is known to differ by sex, we included an interaction term between smoking status and sex in the fully adjusted models for both outcomes.[11] To further explore these potential effect modifications, stratified analyses by sex were used to compare the associations between smoking status and each outcome within each sex group. In addition, we conducted a sensitivity analysis whereby we censored end of follow-up on the 1st of January 2020 to account for the COVID-19 pandemic. Data management was conducted using Stata version 18, and statistical analyses were performed in R version 4.4.3.

Results

A total of 241,624 adults with asthma were included in the study (Figure 1). Of these, 76,746 (31.8%) were never smokers, 117,089 (48.5%) were ex-smokers, and 47,789 (19.8%) were current smokers. Compared to never smokers, current smokers were more likely to be males (43.1% vs 36.2%), be more socioeconomically deprived (33.7% vs 18.0%), have White ethnicity (88.5% vs 73.1%), and have comorbidities (Table 1).

ICS Prescriptions

A total of 151,659 (60.4%) of patients were prescribed at least one ICS in the first year of follow-up. This differed by smoking status whereby 44,636 (58.2%) never smokers, 78,155 (66.8%) ex-smokers, and 28,868 (71.8%) current smokers were prescribed at least one ICS. In the unadjusted model, current smokers were 10% more likely and ex-smokers 44% more likely to be prescribed ICS in the first year of follow-up compared with never smokers (OR=1.10, 95% CI 1.07–1.12 and OR=1.44, 95% CI 1.42–1.47, respectively; Figure 2 and supplementary table 1). After adjusting for baseline covariates, current smokers were 6% less likely and ex-smokers 9% more likely to be prescribed ICS in the first year of follow-up compared with never smokers (OR=0.94, 95% CI 0.91–0.96 and OR=1.09, 95% CI 1.07–1.11, respectively; Figure 2 and supplementary table 1).

A statistically significant sex difference was observed in the association between smoking status and ICS prescriptions (p for interaction = 0.031). Male never smokers had lower risk of receiving ICS prescriptions than female never smokers (OR = 0.93, 95% CI 0.90–0.96; supplementary table 2). However, there was no evidence for a difference between males and females among people who were current or ex-smokers. After stratifying by sex, among females, current smokers had a lower likelihood of receiving ICS compared to never smokers (OR = 0.96, 95% CI 0.92–0.99), while ex-smokers had a higher likelihood (OR = 1.07, 95% CI 1.04–1.10). A similar pattern was observed in males, with effect estimates slightly further from 1.00 than those in females (OR=0.91, 95% CI 0.88–0.95 and OR=1.12, 95% CI 1.08–1.16, respectively). Results remained consistent when end of follow-up was censored on the 1st January 2020 (supplementary table 3).

Asthma Annual Review Visits

A total of 155,436 (63.6%) of patients had at least one asthma annual review visit over follow-up and this varied slightly by smoking status with 49,153 (64.1%) never, 76,498 (65.3%) ex, and 28,382 (59.4%) current smokers. In the unadjusted model, ex-smokers had a higher rate of asthma annual review visits, whilst current smokers had a reduced rate of asthma annual review visits compared to never smokers (IRR=1.05, 95% CI 1.04–1.06 and IRR = 0.87, 95% CI 0.86–0.88, respectively; Figure 3 and supplementary table 4). After adjusting for baseline covariates, both ex-smokers and current

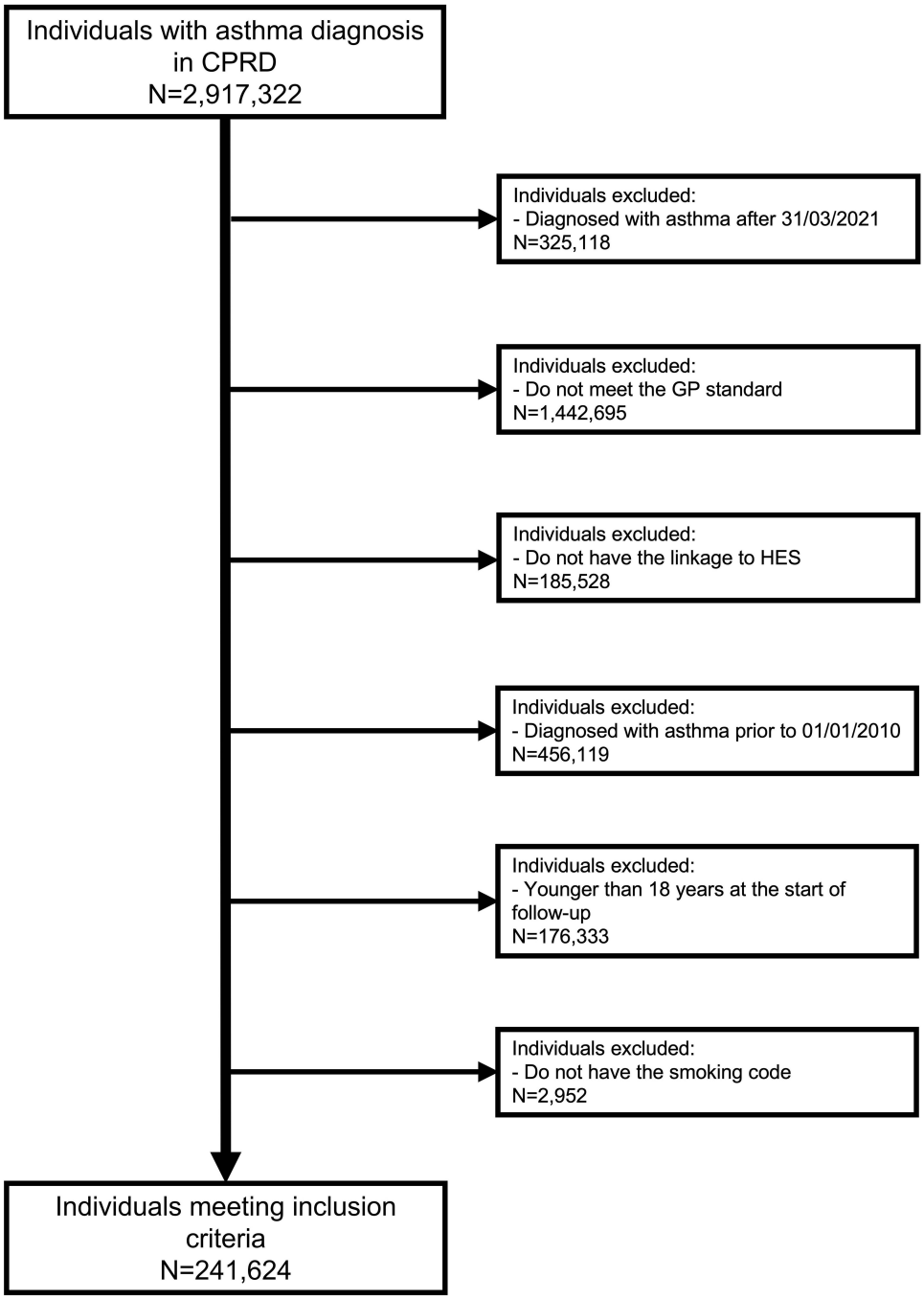

Figure 1 Flowchart illustrating the inclusion and exclusion criteria used to define the final study cohort.

smokers had lower rates of asthma annual review visits compared to never smokers (IRR=0.99, 95% CI 0.98–1.00 and IRR = 0.83, 95% CI 0.82–0.84, respectively; Figure 3 and supplementary table 4).

A significant sex interaction was observed in the relationship between smoking status and asthma annual review visits (p for interaction = 0.029). Among never smokers, males had a significant lower rate of asthma annual review visits than females (IRR = 0.89, 95% CI 0.88–0.91; supplementary table 5). Compared to female ex-smokers, male ex-smokers had a higher rate of asthma review visits (IRR = 1.02, 95% CI 1.00–1.05; supplementary table 5). In contrast, no significant sex difference was detected in the current smoker group (p = 0.631). After stratifying by sex, both female and male current smokers had significantly lower review visit rates relative to never smokers (female IRR = 0.83, 95% CI

Table 1 Cohort Characteristics, Stratified by Smoking Status

Characteristics	Overall N = 241,624	Never Smokers N = 76,746	Ex-Smokers N = 117,089	Current Smokers N = 47,789
Age, Mean (SD)	50.8 (18.0)	45.0 (18.0)	56.4 (17.0)	46.2 (16.1)
Sex, n (%)				
Male	97,623 (40.4%)	27,765 (36.2%)	49,284 (42.1%)	20,574 (43.1%)
Female	144,001 (59.6%)	48,981 (63.8%)	67,805 (57.9%)	27,215 (57.0%)
BMI, Mean (SD)				
	27.4 (5.0)	26.9 (5.0)	28.0 (4.9)	26.6 (5.2)
Missing	23,227 (9.6%)	8,204 (10.7%)	10,226 (8.7%)	4,797 (10.0%)
IMD, n (%)				
1 (least deprived)	45,450 (18.8%)	16,237 (21.16%)	24,284 (20.7%)	4,929 (10.3%)
2	47,202 (19.5%)	15,866 (20.67%)	24,461 (209%)	6,875 (14.4%)
3	46,729 (19.3%)	14,952 (19.48%)	23,450 (20.0%)	8,327 (17.4%)
4	50,479 (20.9%)	15,838 (20.6%)	23,136 (19.8%)	11,505 (24.1%)
5 (most deprived)	51,519 (21.3%)	13,792 (18.0%)	21,634 (18.5%)	16,093 (33.7%)
Missing	245 (0.1%)	61 (0.1%)	124 (0.1%)	60 (0.1%)
Ethnicity, n (%)				
White	202,296 (83.7%)	56,049 (73.1%)	103,943 (88.8%)	42,304 (88.5%)
Black	8,249 (3.4%)	4,227 (5.5%)	2,721 (2.3%)	1,301 (2.7%)
South Asian	19,616 (8.1%)	11,064 (14.4%)	6,352 (5.4%)	2,200 (4.6%)
Mixed	3,197 (1.3%)	1,390 (1.8%)	1,146 (1.0%)	661 (1.4%)
Other	4,117 (1.7%)	2,116 (2.8%)	1,427 (1.2%)	574 (1.2%)
Missing	4,149 (1.7%)	1,900 (2.5%)	1,500 (1.3%)	749 (1.6%)
Depression, n (%)	14,715 (6.1%)	3,429 (4.5%)	6,103 (5.2%)	5,183 (10.9%)
Anxiety, n (%)	7,653 (3.2%)	2,110 (2.8%)	3,348 (2.9%)	2,195 (4.6%)
Breathlessness, n (%)	128,127 (53.0%)	31,420 (40.9%)	68,591 (58.6%)	28,116 (58.8%)
Median Eosinophils (cells/µl) (IQR)	200 (100–320)	200 (100–340)	200 (100–310)	200 (110–300)
Outcome 1, n (%)				
ICS prescription(s) (≥1)	151,659 (60.4%)	44,636 (58.2%)	78,155 (66.8%)	28,868 (71.8%)
Outcome 2, n (%)/Median (IQR)				
Asthma annual review visits (≥1)	155, 436 (63.6%)	49,153 (64.1%)	76,498 (65.3%)	28,382 (59.4%)
Asthma annual review visits*	1 (0–4)	1(0–4)	1 (0–4)	1 (0–3)

Note: Outcome 1 refers to the number of individuals who received ≥1 ICS prescription within one year of their asthma diagnosis. Outcome 2 refers to both the number of individuals who attend ≥1 asthma annual review visits and the number of asthma annual review visits during the follow-up period. *Of those who had at least one asthma annual review visit over follow-up. 144,249 individuals had an eosinophil count.
Abbreviations: SD, standard deviation; BMI, body mass index; ICS, inhaled corticosteroid; IMD, index of multiple deprivation; IQR, interquartile range.

0.82–0.85 and male IRR = 0.83, 95% CI 0.81–0.85). However, the difference between ex-smokers and current smokers in males and females was smaller (female IRR=0.98, 95% CI 0.97–1.00; p=0.014, and male IRR=0.99, 95% CI 0.97–1.01; p=0.275). Results remained consistent when end of follow-up was censored on the 1st January 2020 (supplementary table 6).

Discussion

In this study we investigated the association between smoking status at asthma diagnosis and two asthma management outcomes using electronic healthcare data. Overall, we found that, compared with never smokers, current smokers were less likely to receive ICS prescriptions and had lower rates of asthma annual review visits, whereas ex-smokers were more likely to receive ICS prescriptions but also had lower rates of asthma annual review visits. In addition, we found evidence for sex interactions whereby male never smokers were less likely to receive ICS and have lower rates of asthma annual review visits compared with female never smokers and among ex- smokers males were more likely to attend annual review visits than females.

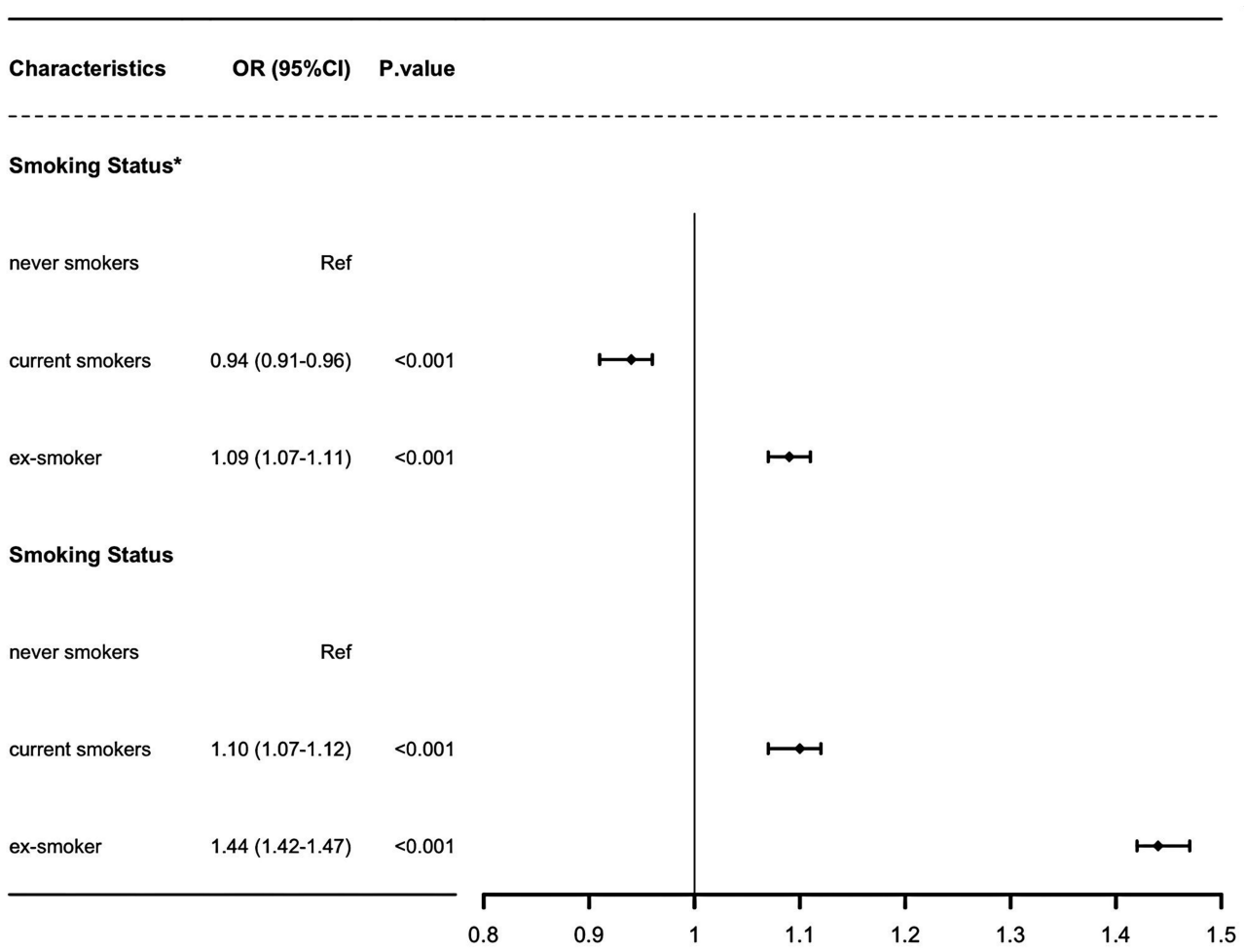

Figure 2 OR and 95% CI were derived from the fully adjusted (Smoking Status*) and crude (Smoking Status) logistic regression model (Supplemental Table 1). The fully adjusted model accounted for age, sex, BMI, IMD, ethnicity, breathlessness, depression and anxiety.
Abbreviations: ICS, inhaled corticosteroid; OR, odds ratio; CI, confidence interval.

Smoking and ICS Prescriptions

To our knowledge, this is the first study to investigate prescribing patterns of ICS in relation to smoking status. We found that current smokers were less likely to receive ICS prescriptions aligns with previous evidence. Earlier research in relation to adherence has reported that smokers with asthma tend to have poorer adherence to ICS and reduced responsiveness in terms of symptom control, lung function improvement, and exacerbation reduction compared with non-smokers.[12] In line with these findings, NICE guidelines also recommend addressing smoking behavior before initiating asthma pharmacotherapy.[13] Specifically, smoking cessation may be required prior to being prescribed ICS as they may be less responsive to corticosteroids.[14] However, delaying the initiation of ICS to prioritize smoking cessation is debated, as postponing treatment may risk worse asthma control.[15] In practice, this balance between promoting smoking cessation and ensuring timely pharmacological treatment remains a challenge in routine care.

Smoking and Asthma Annual Review Visits

Beyond pharmacological treatment, regular asthma annual review visits are also important for disease management. Although the GINA guidelines do not provide specific recommendations regarding asthma annual review visits for patients who smoke, attending these reviews remains essential for all people with asthma.[15] Our findings of lower rates of asthma annual review visits are consistent with previous reports in other respiratory diseases, where patients with COPD or lung cancer delayed seeking care or showed reduced engagement with treatment because they felt their concerns were

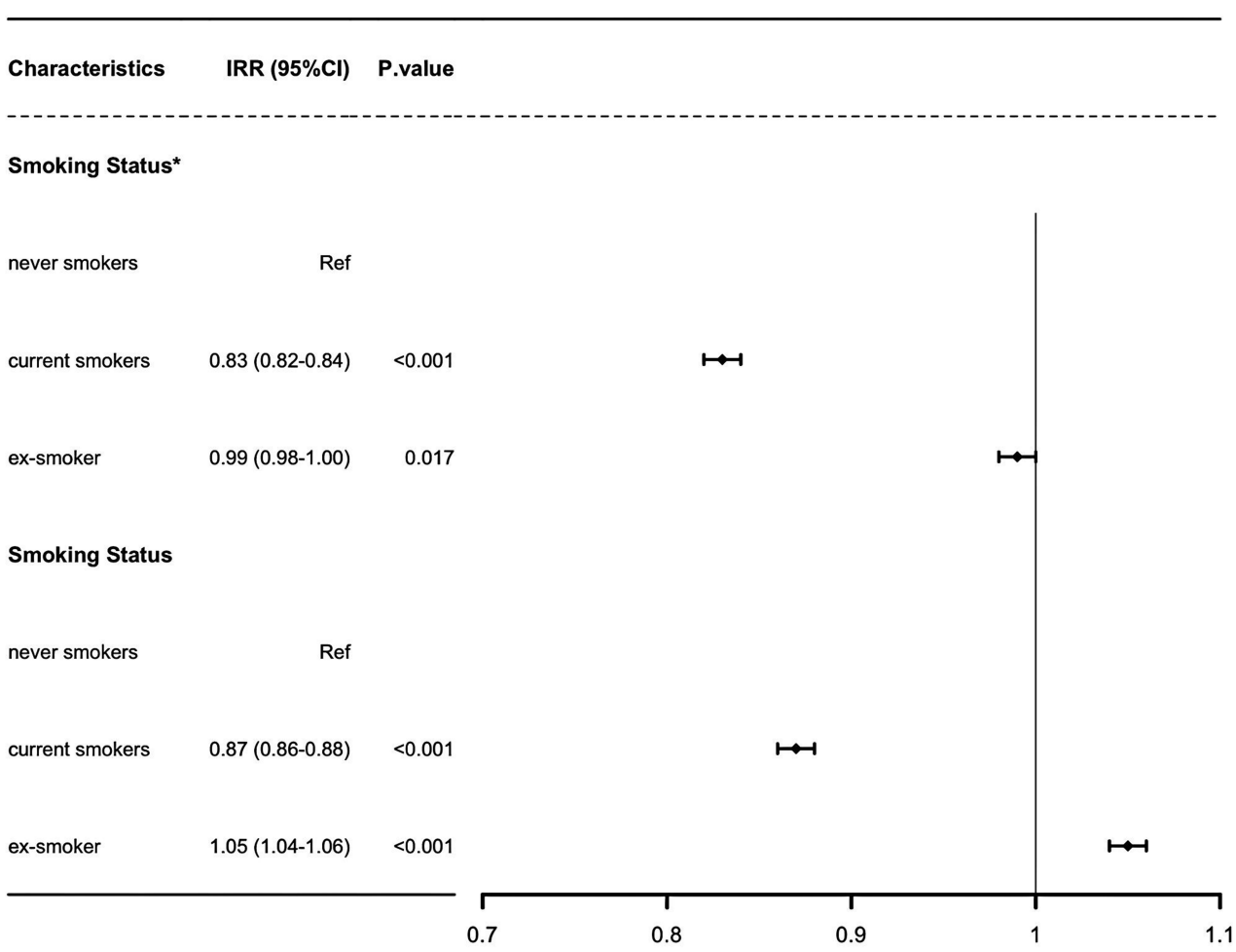

Figure 3 IRR and 95% CI were derived from the fully adjusted (Smoking Status*) and crude (Smoking Status) negative binomial regression model (Supplemental Table 4). The fully adjusted model accounted for age, sex, BMI, IMD, ethnicity, breathlessness, depression and anxiety.
Abbreviations: IRR, incidence rate ratio; CI, confidence interval.

not taken seriously by healthcare professionals or believed they were undeserving of treatment.[16] This may be further compounded in asthma if, as per NICE guidelines, smoking cessation is prioritized first, potentially reinforcing patients' reluctance to engage with treatment.[13] Smokers may also perceive asthma annual review visits as critical or judgmental, which could contribute to lower attendance rates.

Studies have shown that people with asthma who smoke may have poorer disease control and may experience more frequent exacerbations compared with non-smokers.[17,18] Whilst this was not seen in our current study, we did not take into account time-updating changes in smoking status over follow-up whereby patients who were current smokers at asthma diagnosis could have stopped smoking and thus may have been ex-smokers for part of their follow-up. This may have impacted asthma annual review attendance given the outcome was defined over total available follow-up.

Sex Differences in Asthma Management

We observed sex interactions in the association between smoking status and both asthma management outcomes. Consistent with previous studies, sex differences exist in asthma treatment, with females using more medications and being more likely to seek asthma care.[19] However, our findings suggest that these sex differences in asthma management are less apparent among individuals with a smoking history (ex- / current smokers). The attenuation of these differences in people with a smoking history may be related to higher healthcare utilization rates in this group compared with never smokers, although the underlying causes of these differences remain unclear.[20] Further research is warranted to explore

whether these differences are driven by sex differences in healthcare utilization or other unmeasured factors, and how they might be addressed to ensure gender equity in asthma treatment.

Smoking-Related Stigma in Asthma Care

A possible underlying explanation for both lower ICS prescribing and reduced asthma annual review visits could be the experience of stigma. Previous studies have shown that smoking-related stigma exists in both COPD and lung cancer and has been shown to negatively impact patients' willingness to seek care or engage in treatment.[6,21] In relation to asthma, a recent survey-based study found a higher reported prevalence among people who did not use inhaled substances, which may reflect differences in healthcare use or reporting, including potential stigma.[22] In terms of asthma management, no previous studies have investigated the impact of smoking on outcomes however, guidelines state that smoking status, including the use of e-cigarettes, should be assessed prior to initiating or adjusting medications, which may impact prescribing patterns.[21] In addition to patient factors, prescribing patterns may also reflect clinician behaviour; for example, clinicians may be more reluctant to prescribe ICS inhalers to people who smoke, potentially influenced by evidence suggesting reduced treatment effectiveness in this group. Future research incorporating patient-reported questionnaires to assess perceived stigma and healthcare-seeking behavior among people with asthma who smoke would be a valuable direction.

In addition to stigma, other factors may be modifying the relationship between smoking status and management outcomes, such as patient demographics including ethnicity and socioeconomic status. Smoking status is known to differ by ethnicity, which in turn is associated with asthma severity. Previous studies on people with asthma show that a larger proportion of people with non-white ethnicities are never or ex-smokers whereas more people with white ethnicity are current smokers, which is in line with our findings. Despite this, non-white ethnicity is associated with having a more severe asthma phenotype.[23] Further research into understanding how ethnicity, and other factors including socioeconomic status, modify the relationship with asthma outcomes would further our understanding in this field. Finally, whilst most patients in our study had follow-up time that ended prior to the start of the COVID-19 pandemic, rates of asthma annual reviews and ICS prescriptions would likely have declined during the pandemic. Studies have shown that asthma exacerbations declined during the COVID-19 pandemic period, likely due to a combination of patients not having access to healthcare during this time and shielding.[24] This may have also impacted on asthma annual reviews and prescriptions. Our findings from our sensitivity analyses censoring on the 1st of January 2020 were consistent with our main findings suggesting that COVID-19 did not affect differences in rates of asthma annual reviews and the proportion of people prescribed ICS prescriptions by smoking status.

Strengths and Limitations

A key strength of this study is its use of a large, population-based sample from CPRD, which includes over 240,000 individuals and is representative of the English population. This enhances the generalisability of the findings to a broader population of people in England.

Several sources of bias may have affected our findings. First, ICS prescribed within the first year may not truly reflect asthma management given the study period. NICE guidelines (2024–25) for asthma management state that ICS should be prescribed as initial treatment following an asthma diagnosis and future studies should investigate whether this affects management by smoking status.[25] Second, in the fully adjusted models, BMI had a substantial proportion of missing data. Given that the missingness was not evenly distributed across groups, multiple imputation was not considered appropriate as the assumption that BMI is missing at random is not upheld. However, excluding BMI would omit an important confounder, which could also bias the results. We conducted a sensitivity analysis using a LRT to compare model fit between fully adjusted models with and without BMI and model fit was better with the inclusion of BMI, suggesting that retaining BMI in the model was preferable, although residual bias due to missingness cannot be ruled out. Similarly, as routinely collected healthcare data were used, only objective measures were used and healthcare seeking behaviours or perceptions of smoking status and perceived stigma could not be defined. Healthcare seeking behaviors, external to smoking status, could have also influenced the rates of asthma annual review visits. Third, misclassification bias may have been present in our study in relation to the exposure. According to a previous study on UK primary care data, smoking codes are more likely to be missing for ex-smokers or never smokers than for current smokers.[25] This may have introduced information bias and potentially led to an underestimation of the number of non-smokers, however, the

prevalence of smokers and non-smokers in our study was consistent with previous studies. Fourth, whilst we adjusted for a range of variables, including age, sex, BMI, IMD, ethnicity, depression, anxiety, and breathlessness, residual confounding may persist. Whilst blood eosinophil counts are used to classify asthma phenotypes and may impact management outcomes, we did not adjust due to high missingness (40% missing) and the fact that it may be on the casual pathway. Fifth, we defined smoking status based on cigarette consumption rather than e-cigarettes. Given our study period went back to 2010, the number of vapers at asthma diagnosis would have been limited however, as data on vaping becomes more comprehensive, future studies should consider this. Lastly, due to the observational nature of the study, we cannot establish a causal relationship.

Conclusion

This study is the first to investigate the association between smoking status and both ICS prescribing and asthma annual review visit rates. Overall, current smokers were less likely to receive ICS prescriptions and had lower rates of asthma annual review visits compared to never smokers, with sex modifying the effect of smoking status on both outcomes. These findings underscore the need for more equitable and targeted approaches in asthma management, particularly for current smokers, and highlight the importance of considering sex differences when evaluating management patterns. These insights can inform future interventions aimed at reducing treatment gaps and improving outcomes for vulnerable patient populations and should be considered alongside existing smoking cessation policies and programmes to maximize their impact on asthma care.

Data Sharing Statement

Data may be obtained from a third party and are not publicly available. Data sets generated and/or analysed in this study are not publicly available, however, data are available on request from the CPRD. Their provision requires the purchase of a license and this license does not permit the authors to make them publicly available to all. This work used data from the version collected in July 2023 and has clearly specified the data selected in the Methods section. To allow identical data to be obtained by others, via the purchase of a license, the code lists will be provided upon request. Licenses are available from the CPRD (http://www.cprd.com): The Clinical Practice Research Datalink Group, The Medicines and Healthcare products Regulatory Agency, 10 South Colonnade, Canary Wharf, London E14 4PU.

Ethics Approval

A protocol for this research was approved by the independent scientific advisory committee (ISAC) for the UK Medicines and Healthcare products Regulatory Agency (MHRA) Database Research (protocol No 23_003115), and the approved protocol was made available to the reviewers during peer review. This work is based on data from the CPRD obtained under license from the MHRA. Informed consent was not required due to the use of de-identified patient data. The interpretation and conclusions contained in this study are those of the authors alone.

Consent for Publication

All authors have given their consent for publication.

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Disclosure

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