Peertechz

CLINICAL GROUP

OPEN JOURNAL OF Asthma

ISSN: 2640-8082 DOI: https://dx.doi.org/10.17352/oja

Paraskevi Katsaounou[1]*, Marios Ioannou[1], Michael E Hyland[2], Mikaela Odemyr[3], Otto Spranger[4], Anne Lindberg[5], Matthias Gasser[6], Lorena Garcia Conde[7], Xavier Jaumont[7] and Ismail Kasujee[7]

[1]First ICU Evaggelismos Hospital, National and Kapodistrian University of Athens, 15341, Athens, Greece
[2]School of Psychology, University of Plymouth, Devon, United Kingdom
[3]European Federation of Allergy and Airways Diseases Patient's Associations (EFA), Brussels, Belgium
[4]Global Allergy and Asthma Patient Platform (GAAPP), Vienna, Austria
[5]Department of Public Health and Clinical Medicine, Division of Medicine, Umeå University, Sweden
[6]GfK Switzerland AG, Basel, Switzerland
[7]Novartis Pharma AG, Basel, Switzerland

Received: 22 November, 2019
Accepted: 08 December, 2019
Published: 09 December, 2019

***Corresponding author:** Paraskevi Katsaounou, Assistant Professor of Respiratory Medicine, First ICU Evaggelismos Hospital, National and Kapodistrian University of Athens, 20 Evergeti Giavasistr, 15341, Athens, Greece, Tel: +30 6932668142;
Fax: +30 2132043399;
E-mail: paraskevikatsaounou@gmail.com

Keywords: Uncontrolled asthma; Smoking; Quality of life; Smoking asthmatics

https://www.peertechz.com

Research Article

Smoking asthmatics, a neglected large phenotype of asthmatic patients

Abstract

Introduction: Smoking in asthma patients is an important factor contributing to worsened control of asthma. Despite increased awareness of the harmful effects of smoking in patients with asthma, a significant proportion of asthmatics remain smokers. Here, we present findings from the *Still Fighting for Breath* global survey regarding the prevalence of smoking in patients with severe asthma, impact of smoking on asthma control and correlation of smoking with different aspects of quality of life in patients with severe persistent asthma.

Methods: This online survey conducted by GfK Switzerland in 2016 collected data from 1333 adults (>18 years) and caregivers of children (6–17 years) with severe persistent asthma in 9 countries.

Results: Our results showed that smoking was common in asthma patients with 46% of adult patients either current smoker (20%), ex-smoker (24%) or e-cigarette smokers (2%).The proportion of patients with asthma who were current smokers/ ex-smokers or e-cigarette smokers was higher than in the general population in many countries. Overall, 63% of adult patients avoided smoky premises; however, 20% of adults were active smokers .Current smokers with asthma were significantly more frequently diagnosed with anxiety (47%) and depression (41%) than non-smokers (40% and 27%, respectively) and ex-smokers (42% and 28%, respectively). A positive correlation was observed between the number of days that patients with severe asthma used OCS and asthma control according to both the Global Initiative for Asthma (GINA)-defined control (Spearman's *rho*=0.24, *P*<0.001) and patient-perceived control (Spearman's *rho*=0.13, *P*< 0.001).

Conclusion: This survey shows a high prevalence of smoking in patients with severe persistent asthma. Smoking was associated with increased risk of anxiety/depression and show slight increase in use of oral corticosteroid in these patients. These highlight the need for improved strategies for better management of the disease in smokers with severe persistent asthma.

Introduction

Uncontrolled asthma is a subset of asthma that remains inadequately controlled and symptomatic despite treatment with controllers such as high-dose inhaled glucocorticoids, or would need such a treatment to remain well controlled [1,2]. This phenotype of asthma is associated with increased exacerbations, hospitalizations and poorer Quality of Life (QoL).

Uncontrolled asthma can be aggravated by factors such as: co-morbidities including rhinitis, nasal polyposis, bronchiectasis, obesity, osteoporosis, depression and gastroesophageal reflux disease [3-6]. Lack of adherence to treatment, that may result in under-treatment of these patients [7]. Another important factor contributing to worsened control of asthma is smoking, in fact nicotine addiction is considered as a disease according to the Tenth Revision of the International Classification of Diseases and Health Problems (ICD-10) [8]. Smoking may result in worsening of asthma due to accelerated decline in lung function and increased symptoms [5,9]. Based on data from a population–based cohort with 15-year follow-up, Lemmetyinen, et al., suggests that high mortality in asthma patients may be due to smoking-induced excess loss of lung function leading to COPD [10]. Patients with asthma who are current smokers or ex-smokers are at a greater risk of hospitalization and emergency room visits when compared with never smokers [11]. A recent clinical study with a 12 years of follow-up reported a positive correlation between smoking and hospitalization, and a history of ≥20 pack-years was a significant predictor for respiratory-related hospitalization in adult-onset asthma [12]. Furthermore, psychological conditions such as anxiety and depression are often associated

Citation: Katsaounou P, Ioannou M, Hyland ME, Odemyr M, Spranger O, et al. (2019) Smoking asthmatics, a neglected large phenotype of asthmatic patients. Open J Asthma 3(1): 001-008. DOI: https://dx.doi.org/10.17352/oja.000010

with smoking in patients with asthma, which may lead to worsening of the disease [13].

Oxidative stress is known to be involved in the pathogenesis of asthma and to trigger airway inflammation [14]. Asthma patients who smoke are likely to present increased oxidative stress that may incite airway inflammation [14,15]. An early characteristic of asthma is airway inflammation, which if untreated may cause airway-remodeling leading to irreversible airflow obstruction [16]. Cigarette smoking in asthma patients may induce changes in the inflammatory pattern of the airways and asthma phenotype, including increased levels of neutrophils and IL-8 and decreased numbers of eosinophils compared to non-smoking asthma patients. This may lead to accelerated decline in lung function and increased severity of airflow obstruction in these patients [17-19]. These effects may result in reduced efficacy of available treatments in smoking asthmatics.

Treatment with Inhaled Corticosteroids (ICS) is the cornerstone of disease management across different severities of asthma and is recommended in patients with mild-to-severe persistent asthma [20]. However, cigarette smoking in patients with asthma is associated with steroid resistance, increasing asthma symptoms in these patients [21,22]. Studies have shown reduced efficacy of ICS in asthma patients who smoke, in terms of improvement in respiratory symptoms, forced expiratory volume in one second (FEV_1), exacerbation rates and blood markers of inflammation compared with the non-smoking patients [19,21,23,24]. This poor response to ICS in smoking asthma patients is often associated with increased sputum neutrophils level and thus expressing neutrophilic inflammation that is not suppressed by ICS treatment as it suppresses eosinophilic inflammation [25]. Neutrophilia and oxidative stress as an asthma phenotype might be linked with TH17 inflammation and overexpression of IL-17 [26]. Other mechanisms accounting for corticosteroid insensitivity may include increase in tumor necrosis factor levels in smokers [27], which further leads to increase in number of glucocorticoid receptors [28], that have been associated with steroid resistance [21]. Moreover, cigarette smoke impairs histone deacetylase (HDAC) activity [29]. HDAC is recruited by glucocorticosteroids in order to suppress the transcription of inflammatory mediators [29].

High prevalence of psychological disorders, predominantly anxiety and depression have been reported in patients suffering from asthma [30-32]. Previous studies show a strong association between psychological disorders and poor asthma control [6,33,34]. Akula, et al., reported that diagnosis of asthma was associated with a history of mental health disorder, current clinically significant levels of depressive symptoms and a lifetime psychiatric disorder in a community-based study [35]. Psychological disorders may lead to mood disorders that may increase symptom perception in these patients, thus reducing the perception of asthma control [6]. Furthermore, certain symptoms of anxiety and depression such as shortness of breath, insomnia and fatigue may overlap with those of asthma and thus affect the evaluation of asthma control in these patients [36]. A high prevalence of undiagnosed psychological disorders, particularly depression have also been reported in patients with difficult to control asthma, which may increase the risk of deaths due to asthma in these patients [6,37,38].

Passive smoking via exposure to secondhand cigarette smoke may increase the risk of development or augmentation of asthma [39-42]. The prevalence of asthma in men and women is associated with indoor passive smoking exposure at home [43]. Children with asthma exposed to passive smoking experienced worse lung function parameters, more visits to emergency departments, lower oxygen saturation levels on admission, higher scores on the asthma exacerbation severity scale [44]. A study in a large population with 16 years of follow-up showed that passive smoking elevated the risk of developing asthma, even in participants who never experienced active smoking [39]. Furthermore, Hollams, et al., reported that maternal smoking in pregnancy increased the risk of asthma and wheezing in adolescent children [45]. A large Spanish cohort study showed that completely banning smoking in hospitality venues significantly decreased salivary cotinine and reduced the reported respiratory symptoms in hospitality workers. However, other measures like creating smoking areas and partially restrict smoking did not protect these workers against the harmful effects of secondhand smoke [46]. It is interesting that these smoke free laws decrease smoking prevalence in the general population [47,48]. Furthermore, from observational studies it seems that smoke free laws reduce admission rates for asthma in adults and children [49,50]. It is also important that passive smoking is correlated to poor QoL in asthmatic adolescents, something that makes the implementation of these smoke free laws vital [51].

Smoking cessation is an important clinical strategy that can improve clinical outcomes and QoL and reduce total mortality in patients with asthma [10,52,53]. Chaudhuri, et al., showed improvement in lung function and a reduction in sputum neutrophil count in patients who quit smoking (6 weeks after smoking cessation) compared to patients who continued to smoke [54]. Smoking cessation improved clinically important parameters such as airway hyperresponsiveness and symptom score in asthma patients' aged from 19 to 40 years [55].

Despite the harmful effects of smoking on patients with asthma, a significant proportion of asthmatics remain smokers. It seems that it takes HCPs 17 years to convince asthmatics who smoke to quit [56] and that they do not have expertise in smoking cessation and lack engagement in order to help these patients [57]. Studies have shown that the prevalence of smoking among patients with asthma is very similar to that of the general population [58,59]. However, limited data are available on the impact of smoking in patients with severe asthma. Furthermore, smoking asthmatics are often excluded from asthma randomized controlled trials, limiting the information available to assess relative effectiveness of different treatment options for disease management in these patients [60]. Additionally, asthmatic smokers are still not fully aware of the effect of smoking on their disease. Namely, more than 40% believe that smoking does not worsen their asthma [61]. Many believe that the damage has done and therefore, there is little point in attempting to quit smoking or they

Citation: Katsaounou P, Ioannou M, Hyland ME, Odemyr M, Spranger O, et al. (2019) Smoking asthmatics, a neglected large phenotype of asthmatic patients. Open J Asthma 3(1): 001-008. DOI: https://dx.doi.org/10.17352/oja.000010

have never received support for smoking cessation, or raised concern about the perceived health risks of pharmaceutical treatment [62], for smoking cessation.

Here, we present findings from the *Still Fighting for Breath* II global survey [63], regarding the prevalence of smoking in patients with severe asthma, impact of smoking on asthma control and correlation of smoking with different aspects of QoL in patients with severe persistent asthma.

Methods

Participants

Still Fighting for Breath II survey included patients with severe persistent asthma. Adult patients (>18 years) and caregivers of pediatric and adolescent patients (6-17 years) from nine countries were enrolled in this survey. Patients invited to complete the screening questionnaire were mainly identified via databases (consumer panels) [63].

Survey description

Survey description is previously explained in a report by Katsaounou, et al. [63]. For this analysis, specific information on current smoking status was collected among adult patients; individuals were identified as current smoker, ex-smoker, e-cigarette smoker and non-smoker. Questions regarding dual smokers or ex-smokers who were e-cigarette smokers were not included in the questionnaire. Further, among smokers, also number of cigarettes per day was collected among adult patients.

Results

Participants

A total of 1333 patients with severe persistent asthma were surveyed, of whom 1181 were adults and 152 were caregivers of pediatric and adolescent patients; the patient distribution and demographics is previously described in a report by Katsaounou, et al. [63]. The majority of adult patients (56%) were women. The demographics of the population is given in supplementary (S1).

Smoking status

Of the adult patients, 46% were either current smokers (20%), ex-smokers (24%) or e-cigarette (2%) smokers while 54% of patients reported to have never smoked (Figure 1). Interestingly, the proportion of patients with asthma who smoked was higher than that in the general population in many countries (Table 1).

Avoidance of public places

Overall, 63% of adult patients avoided smoky premises; however, 20% of adults were active smokers.

Correlation between smoking and psychological condition

Current smokers with asthma were significantly more frequently diagnosed with anxiety (47%) and depression (41%)

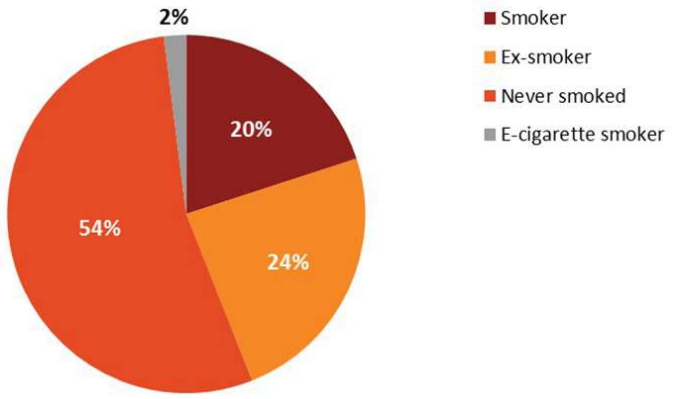

Figure 1: Smoking status of adult patients from the survey.

Table 1: Proportion of smokers in asthmatic and general population.

Country	General population (%) [64]	Asthmatic population (%)		
		Current Smokers	Ex-smokers	E-cigarette smokers
United Kingdom	24.5	24	31	5
Germany	24.5	28	26	4
France	34.1	23	19	2
Italy	19.8	15	36	0
Brazil	14.5	8	18	0
Canada	13.0	25	25	1
Spain	25.4	9	11	2
Japan	18.2	24	22	1
Portugal	22.9	23	20	3

than never-smokers (40% and 27%, respectively) and ex-smokers (42% and 28%, respectively) (z-test, A=0.05).

Contribution of smoking to asthma control and psychological condition

There is a weak effect of smoking on asthma control independently of anxiety/ depression, but this variable does not take into account the degree of smoking that may be of importance. We stress that this survey was not designed to address the issue and we do not have information about the level of smoking in asthma patients (Figure 2).

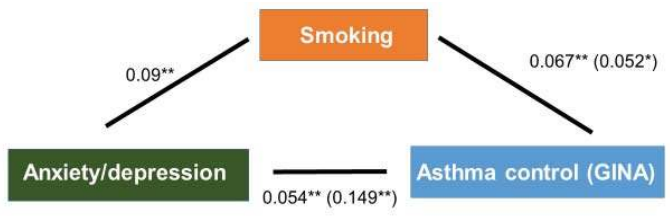

Figure 2: Mediation of analysis between current smoking, anxiety/depression and asthma control. *P=0.055, **P=0.015, ***P<0.001

Mediation analysis: The numbers between the variables is the beta weight in a linear regression, showing the degree of relationship between those variables. The number in brackets between anxiety/depression and asthma control (GINA) is the beta weight between these two variables after removing the

Citation: Katsaounou P, Ioannou M, Hyland ME, Odemyr M, Spranger O, et al. (2019) Smoking asthmatics, a neglected large phenotype of asthmatic patients. Open J Asthma 3(1): 001-008. DOI: https://dx.doi.org/10.17352/oja.000010

common variance of the smoking variable. The number in brackets between smoking and asthma control (GINA) is the beta weight between these two variables after removing the common variance of anxiety/depression.

Oral corticosteroid use: Among adult patients, smokers received treatment with an oral corticosteroid (OCS) for an average of 21 days in the previous 6 months; never-smokers received OCS treatment for 19 days during the same period (Table 2). A positive correlation was observed between the number of days that patients with severe asthma used OCS and asthma control according to both the Global Initiative for Asthma (GINA)-defined control (Spearman's *rho*=0.24, *P*<0.001) and patient-perceived control (Spearman's *rho*=0.13, *P*<0.001).

Discussion

Overall, the survey showed that smoking was common in asthma patients with 46% of adult patients either current smoker, ex-smoker or e-cigarette smokers. A recent report by Pinheiro, et al., shows that former and current smoking is associated with severe asthma. Longer smoking history was observed in the group of patients with severe asthma (former smoker, 4.4 pack-years; current smoker, 25.5 pack-years) when compared with that of those with mild-to-moderate asthma (former smoker, 1.2 pack-years; current smoker,1.3 pack-years) [64]. In our survey, the proportion of patients with asthma who were current smokers, ex-smokers or e-cigarette smokers was higher than in the general population in many countries [65,66]. Previous studies have shown that the prevalence of smoking is similar in general population compared with asthmatic population [67,68]. A cross-sectional retrospective analysis of aggregated data from 11 national severe asthma registries observed that significant proportion of patients with severe asthma also smoke [69]. It should be noted that in our survey, majority of adult patients avoided smoky places, suggesting awareness of the impact of passive exposure to smoking on asthma. Notably, approximately 20% of this population were active smokers.

We found that a higher proportion of patients who were current smokers were diagnosed with psychological conditions such as anxiety and depression when compared with never-smokers [13]. Psychological disorders such as anxiety and depression in patients with asthma are known to be associated with more severe and uncontrolled asthma and to affect the QoL of these patients [6,70]. Our correlation analysis showed that both anxiety/ depression and smoking independently contribute (although weak correlation) to poor asthma control in patients with severe asthma. However, no direct correlation between smoking and depression/ anxiety was observed in our study, which is in line with previous reports [71].

The association between smoking and poor asthma control has been reported; Schatz, et al., reported that smoking was significantly and inversely related to long-term control of asthma [72]. Another survey conducted in asthmatic patients in the US showed that patients who are current smokers report more asthma attacks and nocturnal symptoms compared with non-smokers [5]. Boulet, et al., reported that current smokers are significantly more likely to experience day-time symptoms when compared to former or non-smokers [73]. Furthermore, higher number of smoking pack-years is correlated with more frequent hospitalization and higher number of comorbidities [12]. However, studies have shown that many asthma patients who smoke are not aware or underestimate the contribution of smoking to their worsened asthma symptoms [61,74,75]. Smokers compared to non-smokers report lower scores in recognizing the association between smoking and asthma symptoms [75]. In our survey there is a weak effect of smoking on asthma control independently of anxiety/depression, but this variable does not take into account the degree of smoking, which is important.

Eosinophilic inflammation has been long implicated in the pathogenesis of asthma. However, in addition to eosinophilic inflammation smoking asthmatics show neutrophilic airway inflammation [25]. In fact, Wenzel, et al. (2012) discussed the possibility of considering smoking-induced neutrophilic asthma as a distinct phenotype [26]. Never smokers and ex-smokers with severe asthma express different predictors of frequent exacerbations with higher blood neutrophils observed in ex-smokers and higher blood eosinophils in never smokers. Thus suggesting different types of systemic inflammation pathway play a role in the aetiology of exacerbations in these two groups of patients [76]. Although ICS is an effective treatment option in management of patients with mild-to-severe persistent asthma, studies have reported impaired efficacy of corticosteroids in asthma patients who smoke [23,77,78]. This decreased efficacy may be due to increased oxidative stress as a result of increased neutrophils and macrophages, an innate immune response to cigarette smoke-induced tissue damage [29]. In our survey as well, a slightly higher use of corticosteroids was observed in current smokers compared with never-smokers, indicating greater severity of disease in smokers. This increase in use of corticosteroids may also be attributed to steroid resistance [23]. Higher neutrophil levels is associated with severe airway hyper responsiveness after treatment with ICS in ex- and current smokers with

Table 2: Days of oral corticosteroid use in the previous 6 months by smoking status in adult patients.

Smoking status	United Kingdom	France	Germany	Brazil	Canada	Spain	Italy	Japan	Portugal	Overall
Current Smoker	17	18	28	27	18	12	16	29	22	21
Ex-smoker	17	17	37	21	31	13	20	25	8	23
E-cigarette smoker	13	9	18	0	55	11	0	23	30	18
Never-smoker	21	13	29	19	20	8	21	31	27	19

Citation: Katsaounou P, Ioannou M, Hyland ME, Odemyr M, Spranger O, et al. (2019) Smoking asthmatics, a neglected large phenotype of asthmatic patients. Open J Asthma 3(1): 001-008. DOI: https://dx.doi.org/10.17352/oja.000010

asthma [79]. Furthermore, increase in FEV_1 after 2-week ICS-therapy was observed in patients with lower blood neutrophils [80]. Thus suggesting that higher blood neutrophil levels is associated with less clinical ICS-response in ex- and current smokers with asthma. Chaudhuri R, et al., reported that treatment with OCS for 14 days showed no improvement in lung function in smoking asthmatics compared with a significant improvement in lung function in non-smoker [21]. Schayck, et al., reported that a combination therapy of budesonide/formoterol (160/4.5µg) in patients with asthma who were symptomatic despite treatment with ICS with or without long-acting β_2-agonists (LABAs) showed significant improvement in QoL in terms of Asthma Control Questionnaire (ACQ)-5 scores in non-smokers compared with smokers. However, a higher treatment dose exhibited similar reduction in ACQ-5 scores in smokers and never-smokers [81]. Although cigarette smoking is associated with reduced response to steroid therapy, there is no guideline for optimal pharmacological treatment of smokers/smoking asthmatics. Conventional strategies for disease management include smoking cessation, dose escalation and implementation of laws banning smoking in public spaces [24,46,82].

Fighting for breath survey conducted by European Federation of Allergy and Airways Diseases Patients' Associations (EFA) between 2004 and 2005 reported that passive smoking was considered as one of the major reasons for poor quality of life in patients with severe asthma [66,80,83]. Though various steps have been taken to improve the quality of life of asthma patients including implementation of laws banning smoking in public spaces [84], our survey findings show that smoking still prevails in patients with asthma resulting in poor QoL. Therefore, there is an urgent need to revisit treatment strategies, integration of smoking cessation strategies into asthma care and introduce new treatments for effective management of disease and better quality of life in these patients.

Limitations

This was an online survey, hence the data were self-reported by patients and were not clinically verified; thus, inaccurate responses due to poor recall cannot be excluded. Moreover, it is difficult to accurately predict the actual factors behind participant responses. Our survey was not designed to determine if patients were on the right treatment as per the disease severity and were adherent to treatment, thus influencing their responses. Additionally, the intensity of smoking (pack per day) was not investigated.

Conclusion

Our survey shows that smoking is still common in patients with severe asthma and is associated with increased risk of anxiety/depression and show slight increase in use of oral corticosteroid. Thus, there is a need for improved management and support (smoking cessation, new treatments, assessment of psychological conditions) of smokers with severe persistent asthma.

Acknowledgement

The authors thank Jisha John (PhD) and Rahul Lad (PhD) of Novartis, Hyderabad, India for providing medical writing support/editorial support, which was funded by Novartis, in accordance with Good Publication Practice (GPP3) guidelines.

Funding

The study was funded by Novartis Pharma AG, Basel, Switzerland.

Conflict of interest

MEH, MO, OS, AL, MG have no competing interests. LCG, XJ are employees of Novartis. IK was an employee of Novartis at the time of conduct of the survey. PK was an ERS research fellow in Novartis at the time of the survey.

Supplementary Table 1: Distribution, demographics and disease profile of survey participants by country.

Country	Adults patients	Adolescent patients*	Paediatric patients*	Total
United Kingdom	190	18	11	219
Germany	170	14	10	194
France	170	15	15	200
Italy	116	5	5	126
Brazil	150	10	20	180
Canada	150	3	6	159
Spain	115	4	16	135
Japan	90	-	-	90
Portugal	30	-	-	30
Total	1181	69	83	1333
Male/Female, %	44/56	39/61	27/73	-
Mean age, years				
Male, mean ±SD	42±13.3	14±1.5	8±1.5	
Female, mean ±SD	44±13.6	14±1.8	8±1.8	
Smoking, %				
Current smokers	20	-	-	-
Ex-smokers	24	-	-	-
Never smoked	54	-	-	-
e-cigarette smokers	2	-	-	-
Disease duration, median(years)	16	7	6	-
Proportion of patients diagnosed with allergic asthma, %	52	55	67	53
Proportion of patients diagnosed with non-allergic asthma, %	48	45	33	47

*Data for adolescent and paediatric patients were captured through their caregivers.

Citation: Katsaounou P, Ioannou M, Hyland ME, Odemyr M, Spranger O, et al. (2019) Smoking asthmatics, a neglected large phenotype of asthmatic patients. Open J Asthma 3(1): 001-008. DOI: https://dx.doi.org/10.17352/oja.000010

References

1. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, et al. (2014) International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 43: 343-373. Link: http://bit.ly/2PoS8rp

2. Israel E, Reddel HK (2017) Severe and Difficult-to-Treat Asthma in Adults. N Engl J Med 377: 965-976. Link: http://bit.ly/2PkKuyy

3. Mosen DM, Schatz M, Magid DJ, Camargo CA (2008) The relationship between obesity and asthma severity and control in adults. J Allergy Clin Immunol 122: 507-511. Link: http://bit.ly/33Yc75R

4. DiMango E, Holbrook JT, Simpson E, Reibman J, Richter J, et al., (2009) Effects of asymptomatic proximal and distal gastroesophageal reflux on asthma severity. Am J Respir Crit Care Med 180: 809-816. Link: http://bit.ly/2LyT0ZI

5. Strine TW, Balluz LS, Ford ES (2007) The associations between smoking, physical inactivity, obesity, and asthma severity in the general US population. J Asthma 44: 651-658. Link: http://bit.ly/2YoH6Xq

6. Di Marco F, Verga M, Santus P, Giovannelli F, Busatto P, et al. (2010) Close correlation between anxiety, depression, and asthma control. Respir Med 104: 22-28. Link: http://bit.ly/33SRx6I

7. Lindsay JT, Heaney LG (2013) Nonadherence in difficult asthma - facts, myths, and a time to act. Patient Prefer Adherence 7: 329-336. Link: http://bit.ly/2PmIjuk

8. (WHO) Management of substance abuse. Link: http://bit.ly/2OZh2PF

9. Sergeeva G, Emelyanov A, Leshenkova E, Znakhurenko A, Kozireva L, et al. (2015) Smoking in severe asthma. European Respiratory Journal 46: PA649. Link: http://bit.ly/36foY59

10. Lemmetyinen RE, Karjalainen JV, But A, Renkonen RLO, Pekkanen JR, et al. (2018) Higher mortality of adults with asthma: A 15-year follow-up of a population-based cohort. Allergy 73: 1479-1488. Link: http://bit.ly/2rp4wQh

11. Khokhawalla SA, Rosenthal SR, Pearlman DN, Triche EW (2015) Cigarette smoking and emergency care utilization among asthmatic adults in the 2011 Asthma Call-back Survey. J Asthma 52: 732-739. Link: http://bit.ly/2DVQXKY

12. Tommola M, Ilmarinen P, Tuomisto LE, Lehtimäki L, Niemelä O, et al. (2019) Cumulative effect of smoking on disease burden and multimorbidity in adult-onset asthma. Eur Respir J 54: pii: 1801580. Link: http://bit.ly/2LLcNoX

13. Bush T, Richardson L, Katon W, Russo J, Lozano P, et al. (2007) Anxiety and depressive disorders are associated with smoking in adolescents with asthma. J Adolesc Health 40: 425-432. Link: http://bit.ly/2PoX67x

14. Riedl MA, Nel AE (2008) Importance of oxidative stress in the pathogenesis and treatment of asthma. Curr Opin Allergy Clin Immunol 8: 49-56. Link: http://bit.ly/2PjHcvi

15. Thomson NC, Chaudhuri R, Livingston E (2004) Asthma and cigarette smoking. Eur Respir J 24: 822-833. Link: http://bit.ly/2Rtd6Il

16. Lange P, Scharling H, Ulrik CS, Vestbo J (2006) Inhaled corticosteroids and decline of lung function in community residents with asthma. Thorax 61: 100-104. Link: http://bit.ly/33Yp13E

17. Hillas G, Loukides S, Kostikas K, Simoes D, Petta V, et al. (2013) Increased levels of osteopontin in sputum supernatant of smoking asthmatics. Cytokine 61: 251-255. Link: http://bit.ly/36adP5u

18. Chalmers GW, MacLeod KJ, Thomson L, Little SA, McSharry C, et al. (2001) Smoking and airway inflammation in patients with mild asthma. Chest 120: 1917-1922. Link: http://bit.ly/2YqCoIB

19. Polosa R, Thomson NC (2013) Smoking and asthma: dangerous liaisons. Eur Respir J 41: 716-726. Link: http://bit.ly/354DJYo

20. Global Initiative for Asthma (GINA) (2017) Global strategy for asthma management and prevention. Link: http://bit.ly/33TlmUB

21. Chaudhuri R, Livingston E, McMahon AD, Thomson L, Borland W, et al. (2003) Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma. Am J Respir Crit Care Med 168: 1308-1311. Link: http://bit.ly/2PpxlnX

22. Ricciardolo FL, Di Stefano A (2004) Corticosteroid resistance in smokers with asthma. Am J Respir Crit Care Med 169: 1252-1253. Link: http://bit.ly/38hoQ6H

23. Chalmers GW, Macleod KJ, Little SA, Thomson LJ, McSharry CP, et al. (2002) Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. Thorax 57: 226-230. Link: http://bit.ly/38972uJ

24. Tomlinson JE, McMahon AD, Chaudhuri R, Thompson JM, Wood SF, et al. (2005) Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma. Thorax 60: 282-287. Link: http://bit.ly/2rdEIqv

25. Shimoda T, Obase Y, Kishikawa R, Iwanaga T (2016) Influence of cigarette smoking on airway inflammation and inhaled corticosteroid treatment in patients with asthma. Allergy Asthma Proc 37: 50-58. Link: http://bit.ly/2LwzZXM

26. Wenzel SE (2012) Asthma phenotypes: the evolution from clinical to molecular approaches. Nat Med 18: 716-725. Link: http://bit.ly/2E0iN8F

27. Churg A, Dai J, Tai H, Xie C, Wright JL (2002) Tumor necrosis factor-alpha is central to acute cigarette smoke-induced inflammation and connective tissue breakdown. Am J Respir Crit Care Med 166: 849-854. Link: http://bit.ly/2YA3m0N

28. Webster JC, Oakley RH, Jewell CM, Cidlowski JA (2001) Proinflammatory cytokines regulate human glucocorticoid receptor gene expression and lead to the accumulation of the dominant negative beta isoform: a mechanism for the generation of glucocorticoid resistance. Proc Natl Acad Sci U S A 98: 6865-6870. Link: http://bit.ly/38jJa7R

29. Adcock IM, Barnes PJ (2003) How Do Corticosteroids Work in Asthma?. Ann Intern Med 139: 359-370. Link: http://bit.ly/33TKta5

30. Ciprandi G, Schiavetti I, Rindone E, Ricciardolo FL (2015) The impact of anxiety and depression on outpatients with asthma. Ann Allergy Asthma Immunol 115: 408-414. Link: http://bit.ly/33YqDKK

31. Goodwin RD, Jacobi F, Thefeld W (2003) Mental disorders and asthma in the community. Arch Gen Psychiatry 60: 1125-1130. Link: http://bit.ly/36fXD2J

32. Finnerty J, Paszek G, Sehgal N (2017) P204 Prevalence of anxiety and depression in patients with severe asthma. Thorax 72: A193. Link: http://bit.ly/2LtLQpo

33. Lavoie KL, Cartier A, Labrecque M, Bacon SL, Lemière C, et al. (2005) Are psychiatric disorders associated with worse asthma control and quality of life in asthma patients? Respir Med 99: 1249-1257. Link: http://bit.ly/2DSYgTN

34. Scott KM, Von Korff M, Ormel J, Zhang MY, Bruffaerts R, et al. (2007) Mental disorders among adults with asthma: results from the World Mental Health Survey. Gen Hosp Psychiatry 29: 123-133. Link: http://bit.ly/2RpUyJb

35. Akula M, Kulikova A, Khan DA, Brown ES (2018) The relationship between asthma and depression in a community-based sample. J Asthma 55: 1271-1277. Link: http://bit.ly/2OZYy1n

36. Vieira AA, Santoro IL, Dracoulakis S, Caetano LB, Fernandes AL (2011) Anxiety and depression in asthma patients: impact on asthma control. J Bras Pneumol 37: 13-18. Link: http://bit.ly/2YqFD2J

37. Prins LC, van Son MJ, van Keimpema AR, Meijer JG, Bühring ME, et al. (2015) Unrecognised psychopathology in patients with difficult asthma: major mental and personality disorders. BJPsych Open 1: 14-17. Link: http://bit.ly/2RtqaOb

Citation: Katsaounou P, Ioannou M, Hyland ME, Odemyr M, Spranger O, et al. (2019) Smoking asthmatics, a neglected large phenotype of asthmatic patients. Open J Asthma 3(1): 001-008. DOI: https://dx.doi.org/10.17352/oja.000010

38. Nejtek VA, Brown ES, Khan DA, Moore JJ, Van Wagner J, et al. (2001) Prevalence of mood disorders and relationship to asthma severity in patients at an inner-city asthma clinic. Ann Allergy Asthma Immunol 87: 129-133. Link: http://bit.ly/36e1dtU

39. Coogan PF, Castro-Webb N, Yu J, O'Connor GT, Palmer JR, et al. (2015) Active and passive smoking and the incidence of asthma in the Black Women's Health Study. Am J Respir Crit Care Med 191: 168-176. Link: http://bit.ly/2DSSdi3

40. Kim SY, Sim S, Choi HG (2018) Active and passive smoking impacts on asthma with quantitative and temporal relations: A Korean Community Health Survey. Scientific Reports 8: 8614. Link: https://go.nature.com/2rkabY5

41. Sims M, Maxwell R, Gilmore A (2013) Short-term impact of the smokefree legislation in England on emergency hospital admissions for asthma among adults: a population-based study. Thorax 68: 619-624. Link: http://bit.ly/2DQJ1L0

42. Dahms TE, Bolin JF, Slavin RG (1981) Passive smoking. Effects on bronchial asthma. Chest 80: 530-534. Link: http://bit.ly/2qz1VDa

43. Moon HM, Kim Y, Kwak Y, Kim K (2018) Association between smoking type and prevalence of atopic dermatitis and asthma in men and women. Int J Nurs Pract 24: e12680. Link: http://bit.ly/2OXan8l

44. López Blázquez M, Pérez Moreno J, Vigil Vázquez S, Rodríguez Fernández R (2018) Impact of Passive Smoking on Lung Function and Asthma Severity in Children. Arch Bronconeumol 54: 436-437. Link: http://bit.ly/33Tp9RP

45. Hollams EM, de Klerk NH, Holt PG, Sly PD (2014) Persistent effects of maternal smoking during pregnancy on lung function and asthma in adolescents. Am J Respir Crit Care Med 189: 401-407. Link: http://bit.ly/2rqGQv1

46. Fernández E, Fu M, Pascual JA, López MJ, Pérez-Ríos M, et al. (2009) Impact of the Spanish smoking law on exposure to second-hand smoke and respiratory health in hospitality workers: a cohort study. PLoS One 4: e4244. Link: http://bit.ly/33Zn6vH

47. Lemstra M, Neudorf C, Opondo J (2008) Implications of a public smoking ban. Can J Public Health 99: 62-65. Link: http://bit.ly/2RDTbH5

48. Cesaroni G, Forastiere F, Agabiti N, Valente P, Zuccaro P, et al. (2008) Effect of the Italian smoking ban on population rates of acute coronary events. Circulation 117: 1183-1188. Link: http://bit.ly/2DSLnc2

49. Herman PM, Walsh ME (2011) Hospital admissions for acute myocardial infarction, angina, stroke, and asthma after implementation of Arizona's comprehensive statewide smoking ban. Am J Public Health 101: 491-496. Link: http://bit.ly/350HyO1

50. Naiman A, Glazier RH, Moineddin R (2010) Association of anti-smoking legislation with rates of hospital admission for cardiovascular and respiratory conditions. CMAJ 182: 761-767. Link: http://bit.ly/2LwEKAC

51. Nogueira KT, Silva JR, Lopes CS (2009) Quality of life of asthmatic adolescents: assessment of asthma severity, comorbidity, and life style. J Pediatr (Rio J) 85: 523-530. Link: http://bit.ly/2RsTVyA

52. Jiménez-Ruiz CA, Andreas S, Lewis KE, Tonnesen P, van Schayck CP, et al. (2015) Statement on smoking cessation in COPD and other pulmonary diseases and in smokers with comorbidities who find it difficult to quit. Eur Respir J 46: 61-79. Link: http://bit.ly/2qtdXxI

53. Perret JL, Bonevski B, McDonald CF, Abramson MJ (2016) Smoking cessation strategies for patients with asthma: improving patient outcomes. J Asthma Allergy 9: 117-128. Link: http://bit.ly/2RscRNR

54. Chaudhuri R, Livingston E, McMahon AD, Lafferty J, Fraser I, et al. (2006) Effects of smoking cessation on lung function and airway inflammation in smokers with asthma. Am J Respir Crit Care Med 174: 127-133. Link: http://bit.ly/2DUTl4x

55. Westergaard CG, Porsbjerg C, Backer V (2014) The effect of smoking cessation on airway inflammation in young asthma patients. Clin Exp Allergy 44: 353-361. Link: http://bit.ly/34WauXC

56. Eisner MD, Yelin EH, Katz PP, Shiboski SC, Henke J, et al. (2000) Predictors of cigarette smoking and smoking cessation among adults with asthma. Am J Public Health 90: 1307-13011. Link: http://bit.ly/2Lvn5cA

57. Van Schayck OCP, Williams S, Barchilon V, Baxter N, Jawad M, et al. (2017) Treating tobacco dependence: guidance for primary care on life-saving interventions. Position statement of the IPCRG. NPJ Prim Care Respir Med 27: 38. Link: http://bit.ly/2YpHDs4

58. Bisaccioni C, Aun MV, Cajuela E, Kalil J, Agondi RC, et al. (2009) Comorbidities in severe asthma: frequency of rhinitis, nasal polyposis, gastroesophageal reflux disease, vocal cord dysfunction and bronchiectasis. Clinics (Sao Paulo) 64: 769-773. Link: http://bit.ly/2LwUALx

59. Uchmanowicz B, Panaszek B, Uchmanowicz I, Rosińczuk J (2016) Clinical factors affecting quality of life of patients with asthma. Patient Prefer Adherence 10: 579-589. Link: http://bit.ly/2sP5KVj

60. Apostol GG, Jacobs DR, Tsai AW, Crow RS, Williams OD, et al. (2002) Early life factors contribute to the decrease in lung function between ages 18 and 40: The Coronary Artery Risk Development in Young Adults study. Am J Respir Crit Care Med 166: 166-172. Link: http://bit.ly/2sP5Pbz

61. Wakefield M, Ruffin R, Campbell D, Roberts L, Wilson D (1995) Smoking-related beliefs and behaviour among adults with asthma in a representative population sample. Aust N Z J Med 25: 12-17. Link: http://bit.ly/2RtzpxS

62. Kerr S, Watson H, Tolson D, Lough M, Brown M (2006) Smoking after the age of 65 years: a qualitative exploration of older current and former smokers' views on smoking, stopping smoking, and smoking cessation resources and services. Health Soc Care Community 14: 572-582. Link: http://bit.ly/2qtzCWx

63. Katsaounou P, Odemy M, Spranger M, Hyland ME, Kroegel C, et al. (2018) Still Fighting for Breath: a patient survey of the challenges and impact of severe asthma. ERJ Open Res 4: 00076-2018. Link: http://bit.ly/2DURTPS

64. Pinheiro GP, Souza-Machado C, Fernandes AG, Mota RCL, Lima LL, et al. (2018) Self-reported smoking status and urinary cotinine levels in patients with asthma. J Bras Pneumol 44: 477-485. Link: http://bit.ly/2RtzWjm

65. Katsaounou P, Odemy M, Spranger M, Lindberg A, Hyland ME, et al. (2018) Smoking and severe persistent asthma. Eur Res J 52: PA1230. Link: http://bit.ly/2s51tN4

66. EEIG (2003) Europeans on smoking and the environement: Actions and attitudes. Link: http://bit.ly/2OYVLFz

67. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, et al. (2012) Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health 12: 204. Link: http://bit.ly/2YrsDdl

68. Eisner MD, Yelin EH, Trupin L, Blanc PD (2001) Asthma and smoking status in a population-based study of California adults. Public Health Rep 116: 148-157. Link: http://bit.ly/2DY3L3e

69. van Bragt JJMH, Adcock IM, Bel EHD, Braunstahl GJ, Ten Brinke A, et al. (2019) Characteristics and treatment regimens across ERS SHARP severe asthma registries. Eur Respir J pii: 1901163. Link: http://bit.ly/2Ruy6hW

70. Lomper K, Chudiak A, Uchmanowicz I, Rosińczuk J, Jankowska-Polanska B (2016) Effects of depression and anxiety on asthma-related quality of life. Pneumonol Alergol Pol 84: 212-221. Link: http://bit.ly/34U0DkZ

71. Fluharty M, Taylor AE, Grabski M, Munafò MR (2017) The Association of Cigarette Smoking With Depression and Anxiety: A Systematic Review. Nicotine Tob Res 19: 3-13. Link: http://bit.ly/2PpDuAr

72. Schatz M, Zeiger RS, Vollmer WM, Mosen D, Cook EF (2006) Determinants of future long-term asthma control. J Allergy Clin Immunol 118: 1048-1053. Link: http://bit.ly/38d2seR

Citation: Katsaounou P, Ioannou M, Hyland ME, Odemyr M, Spranger O, et al. (2019) Smoking asthmatics, a neglected large phenotype of asthmatic patients. Open J Asthma 3(1): 001-008. DOI: https://dx.doi.org/10.17352/oja.000010

73. Boulet LP, FitzGerald JM, McIvor RA, Zimmerman S, Chapman KR (2008) Influence of current or former smoking on asthma management and control. Can Respir J 15: 275-279. Link: http://bit.ly/2LtVng4

74. Silverman RA, Boudreaux ED, Woodruff PG, Clark S, Camargo CA (2003) Cigarette smoking among asthmatic adults presenting to 64 emergency departments. Chest 123: 1472-1479. Link: http://bit.ly/343jhpv

75. Heng Ngoh AS, Chen ZJ, Tai CB, Hong Teo SS, Tan NC (2017) Smoking literacy amongst adult Asian asthma patients in primary care. Proceedings of Singapore Healthcare 26: 235-240. Link: http://bit.ly/2LLmmUT

76. Westerhof GA, de Groot JC, Amelink M, de Nijs SB, Ten Brinke A, et al. (2016) Predictors of frequent exacerbations in (ex)smoking and never smoking adults with severe asthma. Respir Med 118: 122-127. Link: http://bit.ly/2YrH8O4

77. Dijkstra A, Vonk JM, Jongepier H, Koppelman GH, Schouten JP, et al. (2006) Lung function decline in asthma: association with inhaled corticosteroids, smoking and sex. Thorax 61: 105-110. Link: http://bit.ly/2OZ5nAe

78. Pedersen B, Dahl R, Karlström R, Peterson CG, Venge P (1996) Eosinophil and neutrophil activity in asthma in a one-year trial with inhaled budesonide. The impact of smoking. Am J Respir Crit Care Med 153: 1519-1529. Link: http://bit.ly/2Rripbq

79. Gafar F, Boudewijn IM, Cox CA, Vonk JM, Schokker S, et al. (2018) Predictors of clinical response to extrafine and non-extrafine particle inhaled corticosteroids in smokers and ex-smokers with asthma. Respir Res 19: 256. Link: http://bit.ly/2quxlul

80. Telenga ED, Kerstjens HA, Ten Hacken NH, Postma DS, van den Berge M (2013) Inflammation and corticosteroid responsiveness in ex-, current- and never-smoking asthmatics. BMC Pulm Med 13: 58. Link: http://bit.ly/2Yulklg

81. van Schayck OC, Haughney J, Aubier M, Selroos O, Ekström T, et al. (2012) Do asthmatic smokers benefit as much as non-smokers on budesonide/formoterol maintenance and reliever therapy? Results of an open label study. Respir Med 106: 189-196. Link: http://bit.ly/2s3c2Ax

82. Gaudreau K, Sanford CJ, Cheverie C, McClure C (2013) The effect of a smoking ban on hospitalization rates for cardiovascular and respiratory conditions in Prince Edward Island, Canada. PLoS One 8: e56102. Link: http://bit.ly/2YraKvl

83. Dockrell M, Partridge MR, Valovirta E (2007) The limitations of severe asthma: the results of a European survey. Allergy 62: 134-141. Link: http://bit.ly/2OY2XBV

84. Areias A, Duarte J, Figueiredo J, Lucas R, Matos I, et al. (2009) Asthma and the new anti -smoking legislation. What has changed? Rev Port Pneumol 15: 27-42. Link: http://bit.ly/38dYPp1

Citation: Katsaounou P, Ioannou M, Hyland ME, Odemyr M, Spranger O, et al. (2019) Smoking asthmatics, a neglected large phenotype of asthmatic patients. Open J Asthma 3(1): 001-008. DOI: https://dx.doi.org/10.17352/oja.000010