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Increased serum cotinine and obesity negatively impact asthma exacerbations and hospitalizations: A cross-sectional analysis of NHANES

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Abstract

Background: Asthma is the most common non-communicable chronic airway disease worldwide. Obesity and cigarette use independently increase asthma morbidity and mortality. Current literature suggests that obesity and smoking synergistically increase asthma-related wheezing. *Objective:* To assess whether increased serum cotinine and obesity act synergistically to increase the likelihood of having an asthma exacerbation, emergency department (ED) visit, or hospitalization. *Methods:* A cross-sectional analysis of the 2011–2015 iterations of NHANES database was performed. Patients aged 18 years or greater with asthma were included. Serum cotinine was utilized as an accurate measurement of cigarette use. Logistic regression models were constructed to determine whether elevated serum cotinine and obesity were associated with self-reported asthma exacerbations, asthma-specific ED usage, and hospitalizations for any reason in the past year. Odds ratios were adjusted for age, gender, race, and ethnicity. Interactions were assessed by multiplying the adjusted effect sizes for elevated cotinine and obesity. *Results:* We identified 2179 ($N = 32{,}839{,}290$) patients with asthma, of which 32.2% were active smokers and 42.7% were obese. Patients with an elevated cotinine and asthma were significantly more likely to have had an asthma-related ED visit in the past year (adjusted odds ratio [AOR] 1.82; 95% CI 1.19–2.79), have a physician-prescribed asthma medication (AOR 2.04; 95% CI 1.11–3.74), and have a hospitalization for any reason (AOR 3.65; 95% CI 1.88–7.07) compared to those with low cotinine. Patients with asthma and obesity were more likely to have an asthma-related ED visit (AOR 1.67; 95% CI 1.06–2.62) or hospitalization for any reason in the past year compared to non-obese patients (AOR 2.76; 95% CI 1.69–4.5). However, a statistically significant interaction between obesity and cotinine was only identified in patients who currently have asthma compared to a previous asthma diagnosis (AOR 1.76; 95% CI 1.10–2.82). There were no synergistic interactions among ED usage or asthma exacerbations. *Conclusion:* Nearly one-third of patients with asthma were current smokers, and almost half were obese. This study identified elevated serum cotinine, a metabolite of cigarette use, and obesity as key risk factors for asthma exacerbations, asthma-related ED visits, and hospitalizations for any reason. Elevated serum cotinine and obesity were not found to act synergistically in increasing asthma exacerbations or ED visits. However, the presence of both risk factors increased the risk of currently having asthma (compared to a previous diagnosis) by 76%. Serum cotinine may be useful in predicting asthma outcomes.

Introduction

Asthma is the most common non-communicable chronic inflammatory airway disease globally [1]. It is characterized by airway hyperresponsiveness, inflammation, and long-term airway remodeling with variable airway limitation [2]. Due to its chronicity, it is associated with poor quality of life, increased risk of repeat acute exacerbations, significant morbidity and mortality, and vast healthcare cost burdens [1,3]. In 2017, there were an estimated 495,100 deaths from asthma and 22.8 million disability-adjusted life years (DALYs) [3]. Financially, asthma exacerbations are a major cause of increased healthcare utilization and higher total healthcare costs for patients and society. In 2007, patients with asthma exacerbations spent an estimated $9223 versus $5011 per person per year, with asthma-specific costs of $1740 versus $847 per person per year, compared with patients without exacerbations [4]. Total expenditures for asthma in 2007 were estimated to be $56 billion per year with productivity losses due to morbidity and mortality of $3.8 and $2.1 billion, respectively [5,6]. Furthermore, patients requiring an

emergency department (ED) visit or hospitalization for asthma are at significantly increased risk for future exacerbations, exposing an ongoing need to prevent these exacerbating events [5].

Most commonly, asthma exacerbations are triggered by certain environmental exposures. The most common viral-associated infection is human rhinovirus, with hospital admission rates for asthma exacerbations in school-aged children and adults correlating with seasonal peaks in rhinovirus infections [7]. Other acute triggers include bacterial infections, environmental allergens, and air pollutants such as tobacco smoke, ozone, and particulate matter [8]. Prevention of exacerbations has been linked to mitigating exposures and triggers, and tailored pharmacologic therapy. The Global Initiative for Asthma (GINA) guidelines were developed and published in 1995 as a collaborative effort between the World Health Organization (WHO) and USA's National Heart, Lung, and Blood Institute with a goal of (1) translating evolving science on asthma into recommendations for the management and prevention of asthma and (2) to stimulate the implementation and evaluation of practical guidelines in order to reduce the global burden of asthma [9].

Following GINA guidelines, as-needed usage of short-acting beta-agonists (SABAs) or inhaled budesonide/formoterol combinations are the first-line treatment for patients with mild intermittent asthma and have been the recommended rescue medication for rapid symptom relief [10]. As symptoms worsen, increased doses of scheduled combination therapies are utilized with monoclonal antibodies as a consideration in the most severe cases.

While these pharmacologic therapies are effective, modifiable risk factors involved in the development of acute asthma exacerbations such as obesity and exposure to cigarette smoke are clinically important targets for improving asthma outcomes. An enlarging body of evidence suggests obesity negatively impacts physiologic parameters in asthma [11]. It is also widely known that cigarette use increases morbidity and mortality in asthma. However, evidence suggests obesity and indoor pollutants such as cigarette smoke may act synergistically, meaning the sum is greater than the added parts, with obesity to increase the likelihood of having asthma as well as symptomatic wheezing [12,13]. Nevertheless, this interaction has not been tested using serum biomarkers to assess for cigarette usage which probed researchers to request evidence of this complex and synergistic interaction between serum biomarkers for cigarettes, obesity, and asthma outcomes [13]. Thus, our objective was to assess the impact of obesity and smoking on asthma exacerbations, ED usage, and hospitalizations with serum cotinine levels, a metabolite of cigarette use. We hypothesized that increased serum cotinine and the presence of obesity would significantly worsen asthma outcomes compared to either variable in isolation.

Methods

Materials

A cross-sectional analysis of the 2011–2015 iterations of the National Health and Nutrition Examination Survey (NHANES) was performed. NHANES is a nationally representative, publicly available database that collects data from non-institutionalized US citizens annually. It is composed of a patient-reported medical questionnaire, physical exam performed by licensed clinicians, and serum laboratory sample collection. Consent was obtained prior to data collection, and resulting information was de-identified prior to being made publicly available. Institutional review board approval was provided by the National Center for Health Statistics.

Subjects

Study inclusion criteria included patients who had a current diagnosis of asthma, age 18 years or greater, provided serum cotinine samples, and completed the physical exam. Persons who had inadequate serum cotinine samples or did not have asthma outcomes documented were excluded. In return for participation, travel expenses and childcare were reimbursed. Data extracted included sociodemographics, serum cotinine levels, body mass index, and asthma outcomes. Measurable asthma outcomes were self-reported and included the following: having had an asthma attack, ED visits for asthma, or hospital visits for any reason in the past 12 months.

Statistical Analysis

Serum cotinine levels were denoted as a categorical variable based on published cotinine cut points with higher than 95% sensitivity and 90% specificity based on race/ethnicity and sex [14]. The cut points varied based on sex, race, and ethnicity. The following cotinine cut points were used: White male (3.26 ng/mL), Black male (7.18 ng/mL), Hispanic male (0.91 ng/mL), White female (5.13 ng/mL), Black female (14.9 ng/mL), and Hispanic female (0.77 ng/mL). Persons with a BMI of 30 kg/m^2 or greater were classified as having obesity. Logistic regression models were developed to assess the impact of serum cotinine and obesity on asthma outcomes. The interaction term between elevated cotinine and obesity was created by multiplying the adjusted effect sizes. Survey design and MEC weightings, provided by NHANES, were used to correct for population-level estimates (N). MEC weightings adjust for complex survey design (oversampling of certain groups), survey nonresponse, and post-stratification adjustments to ensure the calculated estimates are representative of US citizens. Statistical analysis was performed using Stata 16.1 (StataCorp, College Station, TX) in June 2022. Synergy was evaluated mathematically and statistically and, for the purposes of this research, indicates the sum is greater than the added parts (i.e. for $A + B = C$, the effect is additive if $C = A + B$, but is synergistic if $C > A + B$).

Results

We identified a sample of 2,179 ($N = 32{,}839{,}290$) individuals who ever had asthma. Among this group, males were most likely to currently smoke cigarettes (35.36%; $n = 358$, $N = 4{,}813{,}489$) as were Black patients (36.17%; $n = 222$, $N = 1{,}583{,}168$) followed by White patients (30.26%; $n = 353$, $N = 7{,}332{,}677$) as shown in Table 1. Persons aged 30–39 years were most likely to currently smoke cigarettes (36.47%; $n = 142$, $N = 2{,}046{,}822$). The majority of patients had healthcare insurance (84.57%). Finally, persons with obesity and asthma represented 42.74% ($n = 1011$, $N = 13{,}893{,}487$) of the sample.

In patients with a current diagnosis of asthma, 32.15% actively smoke cigarettes ($n = 288$, $N = 4{,}332{,}585$). Among those who currently have asthma and smoke, 28.01% reported having an asthma attack in the past year and 27.71% had an ED visit for asthma in the past year (Table 2). Twenty-one percent of patients with asthma and who currently smoke had a physician-prescribed asthma medication (compared to 78.69% in nonsmokers) and 16.72% were hospitalized overnight for any reason over the previous year.

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Table 1. *Demographics characteristics by cigarette use among individuals ever having asthma*

	Not using cigarettes	Using cigarettes	Total	
	n, N %	*n, N* %	*n, N* %	Design-based Chi-square
Race/Ethnicity				
Hispanic	382, 3041033	124, 1187152	506, 4228186	F (1.69, 79.45) = 2.45, P = 0.10
	71.92	28.08	12.88	
White	689, 16901567	353, 7332677	1042, 24234244	
	69.74	30.26	73.8	
Black	409, 2793692	222, 1583168	631, 4376860	
	63.83	36.17	13.33	
Gender				
Male	555, 8799407	358, 4813489	913, 13612895	F (1, 47) = 9.74, P = 0.003
	64.64	35.36	41.45	
Female	925, 13936885	341, 5289509	1266, 19226394	
	72.49	27.51	58.55	
Age Group				
18–29	364, 5847236	206, 3020356	570, 8867592	F (3.88, 182.39) = 5.4627, P = 0.0004
	65.94	34.06	28.91	
30–39	201, 3565848	142, 2046822	343, 5612670	
	63.53	36.47	18.3	
40–49	212, 3678739	102, 1510497	314, 5189237	
	70.89	29.11	16.92	
50–59	203, 3252226	114, 1840840	317, 5093066	
	63.86	36.14	16.6	
60–69	265, 3612326	95, 1288138	360, 4900463	
	73.71	26.29	15.97	
70+	89, 995466	3, 19525.5	92, 1014991	
	98.08	1.92	3.31	
BMI grouping				
<18.5	14, 253114	18, 242468	32, 495582	F (2.57, 120.98) = 1.91, P = 0.14
	51.07	48.93	1.52	
18.5–24.99	308, 5585200	198, 2848893	506, 8434093	
	66.22	33.78	25.94	
25–29.99	415, 6767751	187, 2919778	602, 9687529	
	69.86	30.14	29.8	
30+	725, 9931251	286, 3962236	1011, 13893487	
	71.48	28.52	42.74	
Insurance Coverage				
Yes	1263, 20110940	511, 7600030	1774, 27710970	F (1, 47) = 24.35, P < 0.001
	72.57	27.43	84.57	
No	211, 2552360	188, 2502968	399, 5055328	
	50.49	49.51	15.43	

Utilizing logistic regression models, persons who had elevated cotinine were significantly more likely to have had an ED visit for asthma in the past year (AOR 1.82; 95% CI 1.19–2.79), have a physician-prescribed asthma medication (AOR 2.04; 95% CI 1.11–3.74), and have a hospitalization for any reason (AOR 3.65; 95% CI 1.88–7.07) compared to patients with low cotinine

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Table 2. *Measured variables among persons with and without cigarette use*

	Not using cigarettes (reference group)	Using cigarettes	Total
	n, N	*n, N*	*n, N*
	%	%	%
Currently have asthma			
No	877, 13406508	391, 5512073	1268, 18918581
	70.86	29.14	58.4
Yes	586, 9142212	288, 4332585	874, 13474797
	67.85	32.15	49.6
Had asthma attack in the past year			
No	395, 6188096	191, 2697776	586, 8885872
	69.64	30.36	47
Yes	481, 7214669	199, 2807453	680, 10022123
	71.99	28.01	53.01
Emergency care visit for asthma in the past year			
No	119, 1345560	78, 876587	197, 2222147
	60.55	39.45	11.75
Yes	758, 12060948	312, 4623871	1070, 16684819
	72.29	27.71	88.25
Physician-prescribed medication for asthma			
No	154, 2235032	72, 999879	226, 3234911
	69.09	30.91	56.05
Yes	114, 1996377	45, 540481	159, 2536858
	78.69	21.31	43.95
Hospital visit			
No	306, 4386457	1008, 15754690	702, 11368233
	27.84	82.28	72.16
Yes	85, 1125616	260, 3163891	175, 2038275
	35.58	16.72	64.42

in the adjusted models (Table 3). Likewise, patients who were obese were more likely to have had an asthma-related ED visit (AOR 1.67; 95% CI 1.06–2.62) or hospitalization for any reason in the past year compared to non-obese patients [AOR 2.76; 95% CI 1.69–4.5 (Table 3)]. While a significant interaction between elevated cotinine and obesity was detected among patients who actively have asthma compared to those who previously had asthma (AOR: 1.76; 95% CI 1.10–2.82), there were no significant interactions between the two dependent variables among patients with asthma that visited an ED for asthma, had an asthma-specific medication, or had an asthma attack in the past year. Interestingly, after applying the interaction term, persons with elevated cotinine and obesity were 62% less likely to have an overnight hospital stay for any reason in the past year (AOR .38; 95% CI 0.19–0.76).

Discussion

We performed a cross-sectional analysis of NHANES, a nationally representative survey, to assess for a synergistic impact between clinical asthma outcomes and increased serum cotinine and obesity. While previous literature has identified an association between these risk factors and asthma outcomes in isolation, this is the first study, to our knowledge, that assesses the interactions of cotinine and obesity on clinical outcomes. Notably, patients with asthma and increased serum cotinine and obesity in isolation had an increased risk of asthma-specific ED usage and hospitalizations for any reason. Persons with increased cotinine and obesity at the same time were more likely to still have asthma, suggesting a synergistic interaction. However, no significant interaction was detected between cotinine and obesity among patients with ED usage, asthma prescriptions, or hospitalizations. These findings provide further support for the deleterious effects of smoking and obesity on asthma-related ED usage and healthcare utilization.

Serum cotinine has a dose-dependent relationship with cigarette exposure and would, therefore, be expected to be more useful than self-reported measures of smoking as a result of social desirability bias or response bias [15]. While it is known that cigarette smoke increases the morbidity of asthma, the present study did not identify a significant interaction effect between obesity, serum cotinine, and asthma outcomes. This synergistic effect was previously suggested by Wu *et al.* [12] and Wong *et al.* [13] Wu *et al.* analyzed data from two cohort studies among children with asthma and

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Table 3. *Associations between asthma symptomology and serum cotinine and obesity category*

	Still having asthma[a]	Having an asthma attack in the past year[b]	Having visited emergency room for asthma in the past year[b]	Dr prescribed medication for asthma[b]	Hospital visit[b]
	AOR (95%CI)	AOR (95%CI)	AOR (95%CI)	AOR (95%CI)	AOR (95%CI)
Cotinine Cutoff					
Below cutoff	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]
Above Cutoff	0.76 (0.55–1.03)	1.05 (0.76–1.46)	1.82 (1.19–2.79)	2.04 (1.11–3.74)	3.65 (1.88–7.07)
Obesity status					
<30 BMI	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]
>= 30 BMI	1.12 (0.85–1.49)	1 (0.73–1.37)	1.67 (1.06–2.62)	0.72 (0.32–1.63)	2.76 (1.69–4.5)
Interaction term with obesity					
Obese × Cotinine	1.76 (1.10–2.82)	–	–	–	0.38 (0.19–0.76)
Sex					
Male	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]
Female	1.76 (1.37–2.26)	1.86 (1.36–2.54)	2.19 (1.28–3.74)	1.03 (0.6–1.77)	1.39 (0.89–2.19)
Age group					
18–29	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]
30–39	1.09 (0.74–1.6)	0.88 (0.55–1.4)	1.07 (0.61–1.86)	1.84 (0.82–4.12)	1.37 (0.79–2.38)
40–49	1.2 (0.75–1.92)	0.98 (0.62–1.53)	0.95 (0.5–1.81)	2.55 (1.06–6.18)	1.15 (0.59–2.25)
50–59	1.67 (1.07–2.62)	1.07 (0.63–1.8)	0.71 (0.35–1.43)	3.13 (1.88–5.21)	0.89 (0.42–1.87)
60–69	1.5 (0.98–2.3)	1.02 (0.68–1.54)	1.01 (0.54–1.91)	2.19 (0.99–4.83)	2.5 (1.39–4.46)
70+	2.9 (1.69–4.99)	0.5 (0.21–1.17)	0.69 (0.27–1.81)	5.69 (0.64–50.81)	6.39 (2.72–15.02)
Race/Ethnicity					
White	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]
Hispanic	0.74 (0.56–.97)	0.86 (0.59–1.25)	2.10 (1.09–4.04)	1.08 (0.53–2.20)	1.68 (1.00–2.81)
Black	1.10 (0.83–1.46)	0.87 (0.62–1.21)	2.61 (1.70)	1.58 (0.73–3.39)	1.62 (1.09–2.41)
Health insurance					
Yes	–	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]
No	–	1.15 (0.81–1.62)	1.15 (0.64–2.09)	0.68 (0.34–1.35)	1 (0.61–1.64)

A. Among individuals ever having a diagnosis of asthma. B. Among individuals still having asthma. Adjusted models controlled for age, gender, obesity status, cotinine cutoff, race/ethnicity, and insurance coverage. AOR: adjusted odds ratio; BMI: body mass index.

noted that urine cotinine and in-home airborne nicotine were both correlated with increased self-reported wheezing and trouble breathing. Wong *et al.* performed a review of current literature among asthma interactions between obesity and indoor/outdoor pollutants (including cigarette smoke) and noted increased reports of asthma symptoms in the presence of all of the mentioned factors. While a positive interaction existed in likelihood of still having asthma among persons with asthma, obesity, and elevated cotinine, it is possible that this effect does not extend to ED usage and asthma-related hospitalizations. Rather, the effect is isolated to only having self-reported wheezing and/or trouble breathing as the previous studies posited.

Interestingly, we identified a lower likelihood of having an overnight hospital stay for any reason among persons with asthma and elevated cotinine and obesity, after adjusting for interactions. We believe that this may be the result of several factors. First, this regression assessed hospitalizations for any reason, rather than for asthma specifically, and may have been impacted by comorbidities that were not controlled. The presence of these other comorbidities may have increased the frequency at which these patients had primary care appointments which helped reduce hospitalizations [16]. Another potential reason for this unexpected finding could be related to stigma. For instance, patients who have both increased serum cotinine and obesity may experience greater stigma than patients with increased cotinine or obesity in isolation which may have resulted in them being less likely to present to the hospital for evaluation. This is supported by the fact that smokers often delay or avoid medical-seeking behaviors as a result of stigma; a finding replicated among obese patients [17,18]. Additionally, misclassification of asthma case definitions may have occurred as survey-based analyses are far from ideal and this survey did not incorporate lung function or asthma severity. Finally,

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disease severity – which was not possible to accurately measure in this study – may have impacted the interaction between cotinine and obesity regarding hospitalizations.

Potential mechanisms underlying the deleterious effects on asthma outcomes by elevated cotinine and obesity are related to the pro-inflammatory cytokines associated with each condition. Obesity and cigarette exposure independently activate nuclear factor kappa B, a transcription factor widely recognized to induce inflammation in the lungs [19,20]. Furthermore, obesity increases pro-inflammatory cytokines IL-6, IL-13, IL-17A, and TNF-α [21–23]. Interestingly, IL-6, IL-17A, and TNF-α are also increased after cigarette smoke exposure, further supporting the potential for a combined interaction between cigarette exposure and obesity on airway hyper-reactivity [24,25].

As a result of the negative health contributions from cigarette use and obesity, public health efforts to reduce their effects are paramount. The most efficacious public health efforts utilize a multimodal approach at the individual, community, and legislative levels. For instance, excise taxation on cigarettes, a result of legislation, has been highly effective at reducing tobacco use in both Africa and the United States [26,27]. Likewise, excise taxes have also been proposed as a method for reducing sugary beverage and alcohol consumption [28], both of which contribute to obesity. At the community level, local leaders have made significant improvements in obesity reduction by utilizing interventions that increase school-based physical activity [29], physical activity utilizing smartphone interventions [30], and diet [31]. Furthermore, the connection between food deserts and obesity is widely recognized with new literature suggesting community involvement, opposed to commercially driven, in supermarket interventions is key to improving these deserts [32]. Finally, public health efforts at the individual level are also useful in reducing obesity and smoking, both of which have been studied in counseling sessions [33,34].

Our study had several strengths and limitations. First, while laboratory specimens were objective measures, ED usage and hospitalizations were self-reported which may have imputed response bias into our analyses. Additionally, the presence of asthma was self-reported, which is not as reliable as a physician's diagnosis of asthma, and may have impacted our findings. The lack of objective lung function measurements also made quantification of asthma severity impossible. This was also a cross-sectional study which prevented the deduction of correlations and only allows for associations to be ascertained. We were also unable to identify cotinine levels by first-hand compared to second-hand smoking exposure. Finally, our exclusion of participants that did not have a serum cotinine value may have confounded our findings. The complex sampling methodology and large sample size with representation across the United States were notable study strengths.

This study identified elevated serum cotinine and obesity as key risk factors for poor asthma outcomes which has been previously understudied. Although we did not identify a synergistic interaction between serum cotinine and obesity on asthma outcomes, the present study highlights the potential usefulness for serum cotinine in clinical practice, particularly when risk-stratifying patients who are highly suspected of smoking nicotine or may be exposed to second-hand smoke in varying degrees. Further research should assess the longitudinal effects of elevated serum cotinine in the setting of patients who have asthma and are obese. Additionally, further research should assess the interaction between risk of hospitalization and concomitant elevation of serum cotinine and obesity.

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References

1. **Jung J, Park HJ, Jung M.** Association between parental cotinine-verified smoking status and childhood asthma: a population-based nationally representative analysis. *Journal of Korean Medical Science* 2021; **36**(30): e193. DOI 10.3346/jkms.2021.36.e193.
2. **Camoretti-Mercado B, Lockey RF.** Airway smooth muscle pathophysiology in asthma. *Journal of Allergy and Clinical Immunology.* 2021; **147**(6): 1983–1995. DOI 10.1016/j.jaci.2021.03.035.
3. **Asher MI, Rutter CE, Bissell K, *et al.*** Worldwide trends in the burden of asthma symptoms in school-aged children: Global Asthma Network Phase I cross-sectional study. *The Lancet* 2021; **398**(10311): 1569–1580. DOI 10.1016/S0140-6736(21)01450-1.
4. **Ivanova JI, Bergman R, Birnbaum HG, Colice GL, Silverman RA, McLaurin K.** Effect of asthma exacerbations on health care costs among asthmatic patients with moderate and severe persistent asthma. *Journal of Allergy and Clinical Immunology.* 2012; **129**(5): 1229–1235. DOI 10.1016/j.jaci.2012.01.039.
5. **Castillo JR, Peters SP, Busse WW.** Asthma exacerbations: pathogenesis, prevention, and treatment. *The Journal of Allergy and Clinical Immunology: In Practice.* 2017; **5**(4): 918–927. DOI 10.1016/j.jaip.2017.05.001.
6. **Barnett SBL, Nurmagambetov TA.** Costs of asthma in the United States: 2002-2007. *Journal of Allergy and Clinical Immunology.* 2011; **127**(1): 145–152. DOI 10.1016/j.jaci.2010.10.020.
7. **Johnston SL, Pattemore PK, Sanderson G, *et al.*** The relationship between upper respiratory infections and hospital admissions for asthma: a time-trend analysis. *American Journal of Respiratory and Critical Care Medicine* 1996; **154**(3 Pt 1): 654–660. DOI 10.1164/ajrccm.154.3.8810601.
8. **Eisner MD, Klein J, Hammond SK, Koren G, Lactao G, Iribarren C.** Directly measured second hand smoke exposure and asthma health outcomes. *Thorax* 2005; **60**(10): 814–821. DOI 10.1136/thx.2004.037283.
9. **Bousquet J, Clark TJH, Hurd S, *et al.*** GINA guidelines on asthma and beyond. *Allergy* 2007; **62**(2): 102–112. DOI 10.1111/j.1398-9995.2006.01305.x.
10. **Papi A, Blasi F, Canonica GW, Morandi L, Richeldi L, Rossi A.** Treatment strategies for asthma: reshaping the concept of asthma management. *Allergy Asthma and Clinical Immunology* 2020; **16**(1): 75. DOI 10.1186/s13223-020-00472-8.
11. **Arismendi E, Bantulà M, Perpiñá M, Picado C.** Effects of obesity and asthma on lung function and airway dysanapsis in adults and children. *Journal of Clinical Medicine Research* 2020; **9**(11): 3762. DOI 10.3390/jcm9113762.
12. **Wu TD, Brigham EP, Peng R, *et al.*** Overweight/obesity enhances associations between secondhand smoke exposure and asthma morbidity in children. *Journal of Allergy and Clinical Immunology Practice.* 2018; **6**(6): 2157–2159.e5. DOI 10.1016/j.jaip.2018.04.020.
13. **Wong M, Forno E, Celedón JC.** Asthma: interactions between obesity and other risk factors. *Annals of Allergy Asthma and Immunology* 2022; **129**(3): 301–306. DOI 10.1016/j.anai.2022.04.029.
14. **Tompkins EL, Beltran TA, Bedno SA.** Differentiating between smokers and nonsmokers using serum cotinine. *Biomarker Medicine* 2019; **13**(12): 1025–1033. DOI 10.2217/bmm-2019-0027.
15. **Rapp JL, Alpert N, Flores RM, Taioli E.** Serum cotinine levels and nicotine addiction potential of e-cigarettes: an NHANES analysis. *Carcinogenesis* 2020; **41**(10): 1454–1459. DOI 10.1093/carcin/bgaa015.

16. **Hu T, Dattani ND, Cox KA**, ***et al.*** Effect of comorbidities and medications on frequency of primary care visits among older patients. *Canadian Family Physician*. 2017; **63**(1): 45–50.
17. **Carter-Harris L.** Lung cancer stigma as a barrier to medical help-seeking behavior: practice implications. *Journal of the American Association of Nurse Practitioners*. 2015; **27**(5): 240–245. DOI 10.1002/2327-6924.12227.
18. **Drury CAA, Louis M.** Exploring the association between body weight, stigma of obesity, and health care avoidance. *Journal of the American Academy of Nurse Practitioners*. 2002; **14**(12): 554–561. DOI 10.1111/j.1745-7599.2002.tb00089.x.
19. **Feng J, Lu S, Ou B**, ***et al.*** The role of JNk signaling pathway in obesity-driven insulin resistance. *Diabetes, Metabolic Syndrome and Obesity*. 2020; **13**: 1399–1406. DOI 10.2147/DMSO.S236127.
20. **Yang SR, Chida AS, Bauter MR**, ***et al.*** Cigarette smoke induces proinflammatory cytokine release by activation of NF-kappaB and posttranslational modifications of histone deacetylase in macrophages. *American Journal of Physiology Lung Cellular and Molecular Physiology* 2006; **291**(1): L46–L57. DOI 10.1152/ajplung.00241.2005.
21. **Dietze J, Böcking C, Heverhagen JT, Voelker MN, Renz H.** Obesity lowers the threshold of allergic sensitization and augments airway eosinophilia in a mouse model of asthma. *Allergy* 2012; **67**(12): 1519–1529. DOI 10.1111/all.12031.
22. **Everaere L, Ait-Yahia S, Molendi-Coste O**, ***et al.*** Innate lymphoid cells contribute to allergic airway disease exacerbation by obesity. *Journal of Allergy and Clinical Immunology*. 2016; **138**(5): 1309–1318.e11. DOI 10.1016/j.jaci.2016.03.019.
23. **Dinger K, Kasper P, Hucklenbruch-Rother E**, ***et al.*** Early-onset obesity dysregulates pulmonary adipocytokine/insulin signaling and induces asthma-like disease in mice. *Scientific Reports* 2016; **6**(1): 24168. DOI 10.1038/srep24168.
24. **Siew LQC, Wu SY, Ying S, Corrigan CJ.** Cigarette smoking increases bronchial mucosal IL-17A expression in asthmatics, which acts in concert with environmental aeroallergens to engender neutrophilic inflammation. *Clinical and Experimental Allergy*. 2017; **47**(6): 740–750. DOI 10.1111/cea.12907.
25. **Crotty Alexander LE, Shin S, Hwang JH.** Inflammatory diseases of the lung induced by conventional cigarette smoke: a review. *Chest* 2015; **148**(5): 1307–1322. DOI 10.1378/chest.15-0409.
26. **Ho LM, Schafferer C, Lee JM, Yeh CY, Hsieh CJ.** The effect of cigarette price increases on cigarette consumption, tax revenue, and smoking-related death in Africa from 1999 to 2013. *International Journal of Public Health*. 2017; **62**(8): 899–909. DOI 10.1007/s00038-017-0980-7.
27. **Apollonio DE, Dutra LM, Glantz SA.** Associations between smoking trajectories, smoke-free laws and cigarette taxes in a longitudinal sample of youth and young adults. *PLoS One* 2021; **16**(2): e0246321. DOI 10.1371/journal.pone.0246321.
28. **Chaloupka FJ, Powell LM, Warner KE.** The use of excise taxes to reduce tobacco, alcohol, and sugary beverage consumption. *Annual Review of Public Health*. 2019; **40**(1): 187–201. DOI 10.1146/annurev-publhealth-040218-043816.
29. **Yuksel HS, Şahin FN, Maksimovic N, Drid P, Bianco A.** School-based intervention programs for preventing obesity and promoting physical activity and fitness: a systematic review. *International Journal of Environmental Research and Public Health* 2020; **17**(1): 347. DOI 10.3390/ijerph17010347.
30. **Kim HN, Seo K.** Smartphone-based health program for improving physical activity and tackling obesity for young adults: a systematic review and meta-analysis. *International Journal of Environmental Research and Public Health* 2019; **17**(1): 15. DOI 10.3390/ijerph17010015.
31. **Trude ACB, Surkan PJ, Cheskin LJ, Gittelsohn J.** A multilevel, multicomponent childhood obesity prevention group-randomized controlled trial improves healthier food purchasing and reduces sweet-snack consumption among low-income African-American youth. *Nutrition Journal* 2018; **17**(1): 96. DOI 10.1186/s12937-018-0406-2.
32. **Brinkley C, Glennie C, Chrisinger B, Flores J.** If you build it with them, they will come. *Journal of Public Affairs* 2019; **19**(3): e1863. DOI 10.1002/pa.1863.
33. **Raman J, Hay P, Tchanturia K, Smith E.** A randomised controlled trial of manualized cognitive remediation therapy in adult obesity. *Appetite* 2018; **123**: 269–279. DOI 10.1016/j.appet.2017.12.023.
34. **Hartmann-Boyce J, Livingstone-Banks J, Ordóñez-Mena JM**, ***et al.*** Behavioural interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database of Systematic Reviews* 2021; **1**: CD013229. DOI 10.1002/14651858.CD013229.pub2.

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