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Beta-Blocker Use is an Independent Risk Factor for Thunderstorm Asthma.

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Abstract

Objective: To identify risk factors for thunderstorm asthma (TA) in subjects ≥15yrs of age from information available in routine clinical records.

Methods: Retrospective and hospital-based case-control study of various clinical factors in all TA cases (n=53) who presented to a single-site emergency department (ED) in November 2016 (TA16) and in a control group of patients (n=156) who presented to the same ED with asthma during the pollen season over eight non-TA years. Bivariate analysis and multivariable logistic regression modelling was performed to calculate the odds of TA asthma in the presence of potential risk factors.

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Results: A logistic regression model revealed that the odds of TA were lower for age (OR: 0.97 95% CI: 0.95 to 0.99), higher for Asian country-of-birth (OR: 4.09 95% CI: 1.40 to 11.95) and higher for oral beta-blocker use (OR: 6.43 95% CI: 1.58 to 26.33) compared to controls. No difference was found between TA16 cases and controls for allergies (to medication, grass pollen, animal), hayfever, smoking, oral non-steroidal anti-inflammatory medications, nor aspirin. Newly diagnosed asthma was higher in TA16 cases versus controls (32.1% vs 12.2%; p=0.001).

Conclusions: Oral beta-blocker medications, younger age and Asian-born heritage are risk factors for thunderstorm asthma. Further study is required to explore the potential association between beta-blockers and TA.

Keywords: Asthma/epidemiology, Asthma/aetiology, Asthma/drug therapy, Adrenergic beta-antagonists/adverse effects, Allergens/adverse effects, Weather, Australia/epidemiology, Disease Outbreaks, Humans

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Introduction

Whilst thunderstorm asthma (TA) has been reported previously[1-5], an unprecedented epidemic event occurred on 21 November 2016 (TA16), in Melbourne, Australia's second largest city of 4.8 million people. Emergency departments (ED) experienced 672% more respiratory-related presentations and 992% more admissions compared to average.[6] Ten deaths were attributed to this TA event and thirty-five patients required intensive care admission.[6] Furthermore, some patients continued to suffer with asthma exacerbation weeks after the event.[7] It is therefore important to understand the risk factors for TA so that these can managed, thereby minimizing the public health and personal impact of future events.

South-eastern Australia is considered at risk of TA owing to populous urban centres, with significant prevalence of asthma and hayfever, surrounded by large areas of rye grass that cause high levels of airborne pollen during the Spring and Summer seasons, which can trigger asthma.[5, 8-13] A general belief is that during pollen season, thunderstorms can significantly increase the levels of airborne pollen, by wind/plume action on ground level pollen, and through osmotic effect break-up pollens into particles which are small enough to bypass the nasal passages and enter the lungs directly, triggering asthma.[9-11] Recent studies of TA16 identified hayfever, asthma, younger age, and Asian

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country-of-birth as risk factors for TA cases presenting to hospital.[7, 13-15] The focus of previous TA studies has been of the aetiological link between pollen exposure, hayfever, pre-existing asthma and TA.[1,5-7,11,13-16] Smoking has been studied and shown not to be a risk factor for TA.[5] Allergies to grasses, moulds, trees and fungi have been studied using sensitisation tests.[5,13,16]

Beta-blockers are frequently prescribed for such indications as hypertension, arrhythmias, cardiac failure and ischaemic heart disease with proven prognostic benefit.[17,18] Against this however, beta-blockers may worsen bronchoconstriction and attenuate the effects of beta-agonists prescribed for asthma.[19] The literature reports that beta-blockers are generally considered safe in asthma, however they may be associated with asthma exacerbations and are contra-indicated in unstable asthma.[20,21]Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) are also associated with asthma exacerbation, due to their pharmacological action on prostaglandin metabolism resulting in airway inflammation and bronchoconstriction.[22-24] The effects of these drugs in TA are not described. Because TA is characterised by acute allergen-induced bronchoconstriction, we hypothesised that beta-blockers, aspirin and/or NSAIDs were independent risk factors for TA.

Methods

The Epworth Richmond ED is part of Epworth HealthCare, a not-for-profit private health group, and treated 29200 patients from 1/7/2017 to 30/6/2018. It is located in the suburb of Richmond, 3.2 kilometres from the centre of Melbourne. This study was approved by the Epworth HealthCare Ethics Committee.

TA cases were defined as having attended Epworth Richmond ED following the thunderstorm on the evening of 21 November 2016 with a new-onset of, or an exacerbation of existing, asthma. All cases

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were reviewed by emergency clinicians and included for study if notes indicated acute onset, or worsening, of symptoms compatible with a diagnosis of asthma, including any of dyspnoea, wheeze, or chest-tightness not found to be due to another cause. Patients with chronic obstructive airways disease were excluded.

The control group comprised all asthma cases that attended Epworth Richmond ED during the Melbourne pollen season[25], from October 22nd to December 31st, in the years 2008 to 2017 (excluding both 2010 and 2016 when epidemic TA occurred. On 25 Nov 2010, 18 patients presented with TA to the ED). These years were selected to have sufficient control cases to meet sample size estimates, discussed below. A diagnosis of asthma as entered into our patient management system flagged possible controls and the diagnosis was confirmed based on the clinician's medical record showing asthma as a primary diagnosis. Patients with chronic obstructive airways disease were excluded.

Latent asthma was defined as a patient who had not experienced asthma for over five years. New onset asthma was defined as a patient who had no prior history of asthma. Chronic asthma was defined as a patient having a past history of asthma, temporally distinct from the ED episode, who did not meet the latent or new-onset asthma definition.

Epworth Richmond ED opened a new paediatric section in February 2016. The average daily ED attendances of patients below 15 years of age increased after opening. Therefore, to control for this change in business, paediatric patients <15 years of age were excluded from study.

Data on the age, gender, nationality/place of birth were obtained from the patient management system. These data were entered by nursing and clerical staff at the time of presentation of the patient. Emergency doctors conducted a retrospective review of patient and medication charts for

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collection of data on past medical history of asthma and/or hayfever, and whether aspirin, oral non-steroidal anti-inflammatory drugs and/or oral beta-blocker drugs were taken prior to the episode of asthma that instigated the ED attendance. Where a patient had previously been to Epworth HealthCare, prior attendance-related documentation was studied to ascertain whether there was documentation of smoking status, asthma or hayfever. Data were entered by the authors into a Microsoft Excel spreadsheet.

Sample size

The sample size required to detect an odds ratio as large as 3 (or as small as 1/3, as reported in Girgis et al 2000[5], for 30% medication use among controls) was calculated. An effect of this size could be detected at the 5% level of statistical significance with statistical power of 80%, and using two controls per case, if at least 46 cases and 92 controls were recruited. Sample size calculations were conducted using OpenEpi version 3 software (http://www.openepi.com/SampleSize/SSCC.htm), for a case-control study employing the method of Kelsey et al. [26,27]

Approximately 50 persons presented with asthma to Epworth Richmond ED on 21 November 2016, therefore, the chart notes and other relevant information of twice as many controls as cases, or at least 50 cases and 100 controls would be required.

Statistical analysis

Statistical analysis of binary outcome or dependent variables, such as whether or not the patient was born in Asia, had a history of asthma or hayfever, beta-blocker and aspirin/NSAID use, was performed using binary logistic regression, with control versus TA16 as the grouping or independent variable. Exact logistic regression was employed for NSAID use due to zero frequencies (no TA16

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case took NSAID).[28]Analyses of medication were adjusted for age as a possible confounder, due to the association between age and medication. Other analyses were unadjusted. There was a total of 206 persons and 209 presentations, with 3 (1.5%) persons (2 controls, and 1 TA16) presenting twice (other attendance being in control period). Preliminary analyses allowing for potential clustering using robust standard errors, [28] due to the small number of repeated presentations, made very little difference to the results. Therefore, only analyses that did not take potential clustering into account were reported.

Based on previous work[5-7,13-15], a small number of factors were examined in a multivariable logistic regression with control versus TA16 as the outcome variable and the following as independent variables: age (found by preliminary graphic analysis to be approximately linearly related), gender, born in Asia, past history asthma, past history hayfever, beta-blocker and aspirin or NSAID use. Aspirin and NSAID use were combined for analysis due to their low frequencies.

All statistical analyses were conducted using Stata 15 (Stata Corporation, College Station, Texas, 2017).

Results

One hundred and fifty-six controls and 53 cases in the TA16 event were studied. Six paediatric asthma cases were excluded from the TA16 event and twenty-five paediatric asthma cases were excluded from the control group. Table 1 shows the bivariate analysis of possible risk factors for TA16 cases versus controls. Figure 1 provides a boxplot of age distribution.

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TA16 cases had a higher odds of taking an oral beta-blocker than the controls, controlling for age (unless specified, results are unadjusted) (OR: 6.08 95% CI: 1.62 to 22.88, p = 0.007), with similar results being obtained using exact logistic regression. Table 2 shows the characteristics of the patients in the control and TA16 groups taking oral beta-blockers.

There was no difference, when controlling for age, for TA16 cases on NSAIDs (5.8% of controls vs 0% of TA16, exact logistic regression, OR = 0.35, 95% CI = >0.0 to 2.36, p = 0.33) or on aspirin (5.8% of controls vs 3.8% of TA16, OR = 1.12, 95% CI = 0.21 to 5.81, p = 0.90) compared to controls. There were no significant differences in self-reported grass pollen allergy, any allergies to medications, foods, or animals, smoking status (ever smoked) between TA16 cases and controls

As shown in Table 3, when several clinically-chosen key variables (age, male gender, whether or not born in Asia, past history of hayfever, past history of asthma, whether or not taking a beta-blocker and whether or not taking aspirin or NSAIDs), were simultaneously entered into a multivariable logistic regression model, with group (controls vs TA16) as the outcome, younger age, being born in Asia and taking a beta-blocker were associated with TA16. Specifically, each year increase in age was associated with a 3% decrease (1 - the odds ratio of 0.97) in the odds of TA. Each ten year increase in age would therefore be associated with a 26.3% (1.0 - exp(10 * log(0.97) = 1.0 - 0.737) decrease in the odds of TA.

Discussion:

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In this study we compared the characteristics of two groups of patients who presented to the ED with asthma: a group that presented in relation to a thunderstorm event in 2016 and a control group of patients who presented during the pollen season in non-thunderstorm asthma years.

Oral beta-blocker medications were identified in this study as a risk factor for TA16, a finding not previously reported in the literature. Some studies have shown that beta-blockers (both cardioselective[21] and non-cardioselective[20,21]) are associated with an increased risk of asthma exacerbations. There are however no studies reported in the literature as to whether beta-blockers predispose to exacerbations of asthma in patients exposed specifically to high levels of airborne pollen. Interestingly, beta-blockers have been associated with fatal reactions in subcutaneous allergen immunotherapy.[29] It is possible therefore that with the potent stimulus akin to the allergen challenge that occurs during thunderstorm asthma,[30] beta-blockers may worsen underlying lung function and impair the response to beta-agonist rescue therapy, precipitating or exacerbating allergenic asthma in susceptible individuals. This may explain the association we found between beta-blocker use and ED attendance with TA. Beta-blockers may therefore be a modifiable risk factor for TA in asthmatics. In non-asthmatics, TA is unpredictable, however other studies report that 41-53% of "non-asthmatics" in TA16 had probable undiagnosed asthma.[6,7,13] Hence, if clinicians screen for and diagnose asthma, beta-blockers may also be a modifiable risk factor for TA in some "non-asthmatics." Another possibility is that patients sought ED care because of concern related to comorbidities for which the beta-blockers were prescribed. Overall however, the wide confidence interval and low numbers in our study limit the generality of our finding of the association of TA with beta-blocker use, and hence further study is required with a larger sample size and/or a prospective study with planned data collection in future events.

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There was no association found between TA16 cases and aspirin, nor NSAIDs, a finding not previously reported in the literature. Aspirin/NSAIDs tend to lead to acute exacerbations of asthma in susceptible patients.[24] Some patients are unaware that they are sensitive to aspirin/NSAIDs until they undergo provocation tests.[24] Considering this, we found no evidence that TA16 cases attended the ED as a result of aspirin/NSAID intake nor of added susceptibility to TA arising from aspirin/NSAID intake.

Similar to previous reports, younger age[6,7,15] and being born in an Asian country[6], were also found to be risk factors, whilst smoking was not found to be a risk factor.[5] Hayfever prevalence is significantly greater in Asian born immigrants compared to non-Asian born Australians and increases with the length-of-stay in Australia.[31] Such a high prevalence of hayfever potentially confers an increased risk for TA.[1, 7,11,13-16]

The proportion of patients with reported hayfever in our study was higher in TA16 cases compared to controls, but this was not statistically significant. Previous studies found a much higher prevalence of hayfever in TA cases compared to our study (87-100% vs 43%).[5,7,13-16] This is most likely due to the strength of the survey and skin-prick testing methodology these studies employed to diagnose hayfever. For example, one study found 28% of TA cases were classified as having mild hayfever,[7] a group theoretically less likely to be diagnosed in the clinical environment of an ED due to there being a bias favouring detection of the more severe spectrum of hayfever, either arising from clinician questioning and/or patient experience. Therefore, the results of our study suggest that hayfever is probably underdiagnosed in the ED. Future research may consider how diagnostic tools, such as validated questionnaires, could assist ED physicians.

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In this study we found that TA cases had a lower prevalence of a past history of asthma compared to controls (68% of TA16 cases vs 88% of controls), a finding similar to that reported in a case-control study of a TA event in the regional city of Wagga Wagga in 1997 (64% of TA cases vs 82% of controls).[5] However, compared to the findings of other studies of the TA16 event, the TA16 cases who attended Epworth Richmond ED had a higher prevalence of a past history of asthma (68% vs 37-43%), as did the TA cases studied in the Wagga Wagga event (64% vs 37-43%).[5,7,13-15] Therefore, conversely, the prevalence of newly diagnosed asthma was lower in the Wagga Wagga TA event (36%) and in our TA cohort (32%) , compared to the TA16 cases investigated in other studies (57-63%).[5,7,13-15] The scale of the Wagga Wagga TA event was much smaller than the TA16 event and this may explain why there was a lower prevalence of newly diagnosed asthma found in the study of that event[5] compared to studies of the TA16 event.[7,13-15] It is unclear however why TA16 cases in our study also had a lower prevalence of newly diagnosed asthma compared to TA16 cases investigated in other studies. [7,13--15] Patients may have returned to our ED in TA16 because of an affiliation arising from past attendances for asthma. The studies of TA16 are all based on public-sector ED attendances.[7, 13-15] Compared to private EDs there are more public sector EDs in Melbourne. Therefore, new-onset asthmatics were more likely to be near and/or familiar with a public sector ED and thereby sought emergency care within those facilities. The inner-city location of our ED may have been a factor. Of the TA16 cases who attended public sector EDs, 25%-33% had undiagnosed asthma,[7,13-15] which our study did not specifically explore. Socioeconomic factors may be a confounder in a patient's decision to attend a private ED and the likelihood of having asthma diagnosed and controlled through health awareness, education and regular visits to a general practitioner.

Limitations:

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Limitations of the study include that it is a retrospective, single site study, with a comparatively small sample size. Epworth Richmond Hospital cares for a significant cardiovascular casemix and this may potentially have biased the finding of beta-blocker association with TA16. Some asthma cases from the control group may also have had asthma triggered, or worsened by thunderstorm activity, although inhaled corticosteroid use may also have protected them from ED presentation with TA.[32] Our study population may not be representative of the overall TA cases. The wide confidence intervals of our results places some uncertainty on the size of the associations. The low frequency of medication use also means that our results should be interpreted with caution. Further study is required with larger sample sizes and/or planned collection of relevant data prospectively in future events

Conclusion:

In summary, this study identified oral beta-blockers, younger age and an Asian country of birth as independent risk factors for the Melbourne TA event in 2016. Further study would help understand the potential risk of beta-blockers in thunderstorm asthma.

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Disclosure

This project received no funding.

Competing Interests

Dr Sutherland has received speaker and advisory board honoraria from Astra-Zeneca, Novartis and Stallergenes. Dr Nimorakiotakis has received a speaker honorarium from Astra-Zeneca.

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Table 1: Bivariate Analysis of Possible Risk Factors for Thunderstorm Asthma 2016.

		Control (n=156)	Thunderstorm Asthma 2016 (n=53)	Odds Ratio or difference between means TA16 vs Control (95% CI)	P value TA16 vs Control
Male					
	n	55	30	**2.40 (1.27 to 4.52)**	**0.007**
	%	35.3%	56.6%		

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AGE(yrs)				
Mean			**-10.0 (-16.3 to -3.8)**	**0.002**
Median	48.7	38.6		
(Standard Deviation)	47.5 (20.3)	32 (18.6)		
Born in Asia				
n	10	10	**3.40 (1.33 to 8.69)**	**0.011**
%	6.4%	18.9%		
Past history asthma			**0.29 (0.14 to 0.62)**	**0.001**
n	137	36		
%	87.8%	67.9%		
Past history hayfever			1.37 (0.73 to 2.58)	0.332
n	56	23		
%	35.9%	43.4%		
On oral beta-blockers			**6.09 (1.62 to 22.88)†**	**0.007**
n	7	6		
%	4.5%	11.3%		
On Aspirin or NSAID				
n	14	2	0.89 (0.07 to 3.32) †	0.894
%	9.0%	3.8%		

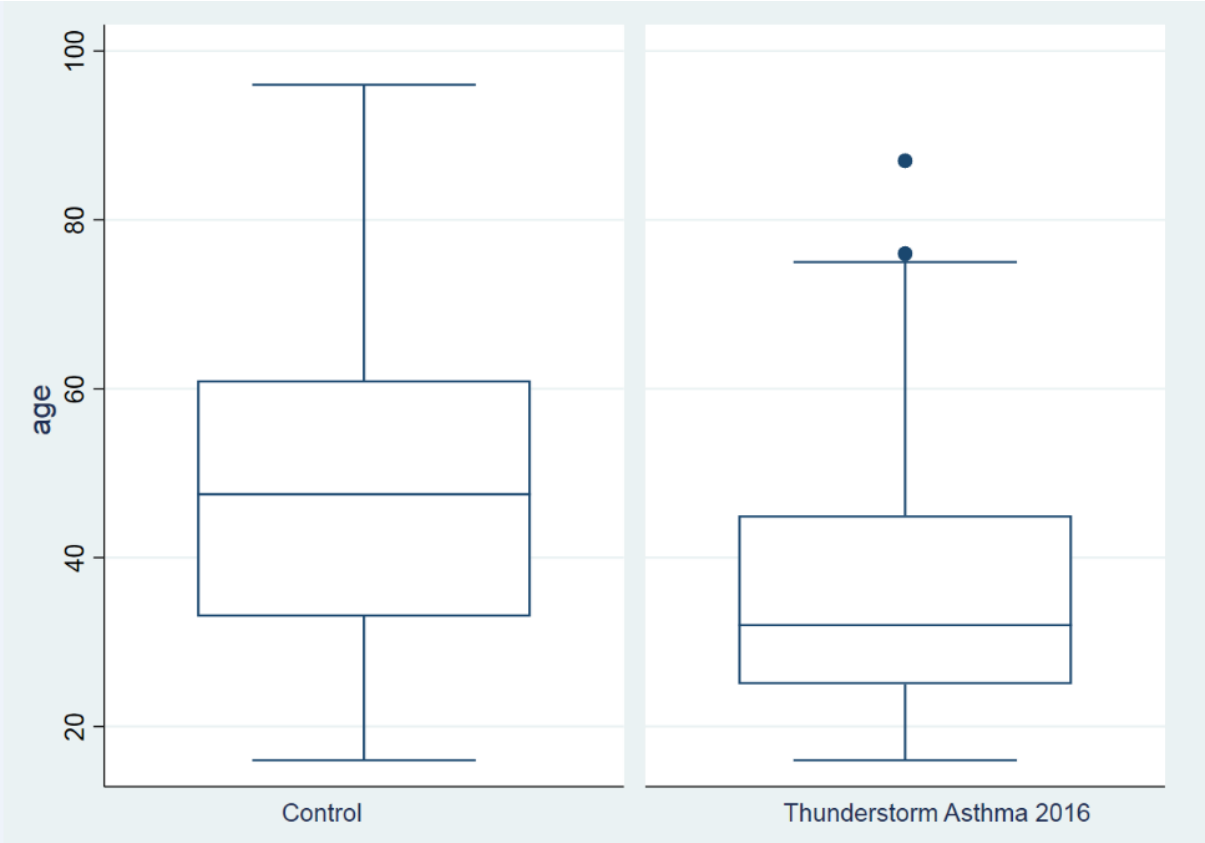
† adjusted for age

Figure 1. Age distribution

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Table 2. Characteristics of Patients taking oral Beta-Blockers

	Controls (n =7)	**Thunderstorm Asthma 2016** (n =6)
Gender-Male	2	2
Age		
Mean	68.1	65
Median	69	68.5
Standard Deviation	10.9	18.5
Range	31-87	54-81
Beta-Blocker Type		
Cardioselective-total	7	4
Atenolol	4	2
Bisoprolol	1	1
Metoprolol	2	1
Non-cardioselective-total	-	2
Propranolol	-	2
Indications		
Hypertension (HT)	5	4
Ischaemic Heart Disease (IHD)	2†	1
Hypertrophic cardiomyopathy (HCM)	-	1
Asthma Type		
Chronic	6 (HTx5, IHD)	2 (IHD, HT)
Latent	0	1 (HT)
New-onset	1 (HT)	3 (HT x2, HCM)

†both cases also had past history atrial arrhythmias

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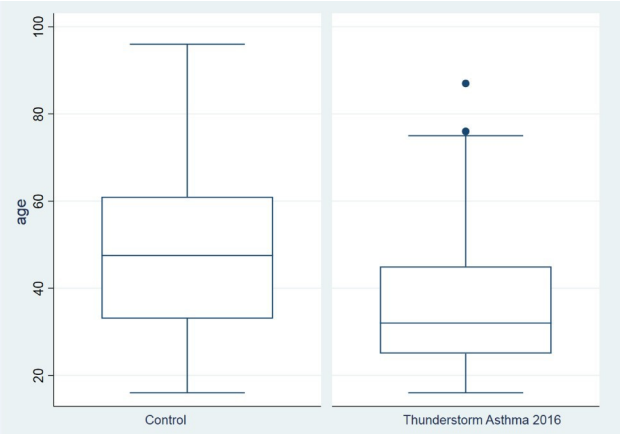
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Table 3: Multivariable Logistic Regression Model for TA16 vs Controls

Variable	Odds Ratio	95% Confidence Interval	p
Age	**0.97**	**0.95 to 0.99**	**0.002**
Male gender	1.78	0.88 to 3.62	0.109
Born in Asia	**4.09**	**1.40 to 11.95**	**0.010**
Past hayfever	0.90	0.44 to 1.85	0.771
Past asthma	0.45	0.20 to 1.01	0.054
On oral beta-blockers	**6.43**	**1.58 to 26.33**	**0.010**
On Aspirin or NSAID	0.49	0.07 to 3.52	0.482

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Thunderstorm Asthma. An Emergency Department Experience of Two Events.

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