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Review article

Which came first, the risk of migraine or the risk of asthma? A systematic review

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ABSTRACT

Objectives: We conducted this review to systematically assess the association and risk of the migraine in the patient with asthma and vice versa.
Methods: We systematically searched publishes articles indexed in PubMed, Scopus, Cochrane library, PsycINFO, CINAHL, ISI Web of Science, Science Direct from inception, and Embase databases until June 2017. The quality assessment of the involved studies was done using the Newcastle-Ottawa Scale (NOS).
Results: Eight studies with 389,573 participants were reviewed and selected for data extraction. Among the selected studies, 5 were reported the association between migraine with asthma risk, and the rest three studies reported the risk of asthma in patient with migraine compared to non-moraine individuals. Odds ratio (OR) of migraine for patient with asthma as compared with non-asthmatic individuals was 1.62 (95% CI 1.43–1.82). Data pooling using a random-effect model showed that migraine was associated with a significant increased risk of asthma (relative risk (RR): 1.56; 95% CI: 1.51–1.60; $p < .00001$). Besides, sub-group and sensitivity analyses supported the positive association between asthma and migraine, and risk of asthma in migraine patients.
Conclusion: Now it is unknown if control of the asthma will impact the severity of migraines or vice versa, but it is necessary to perform more research to further explain the mechanisms through which asthma increases the frequency of migraine or vice versa. If two conditions linked, once an individual undergo better control of asthma symptoms, might the excruciating migraine ease, too.
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Abbreviations: MOOSE, meta-analysis of observational studies in epidemiology; PRISMA, preferred reporting items for systematic reviews and meta-analyses; NOS, Newcastle-Ottawa Scale; OR, odds ratio; RR, relative risk or risk ratio; HR, hazard ratio; CI, confidence interval.

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1. Introduction

Asthma is one of the most common chronic diseases of airway with clinical respiratory *symptoms* such as *chronic* inflammation, irritability and lung stenosis [1]. Epidemiology of asthma is important due to increased prevalence and severity, as well as poor asthma control leads to socio-economic and burden control costs impacts on health-care systems [2]. The prevalence of asthma varies widely among different countries, and is continuing to rise over the last decades in both industrialized societies and developing countries [3–5]. Despite the fact that the prevalence of asthma symptoms has increased over the past 30–40 years, there is a horizontal curve in developed and industrialized countries, and despite the fact that the percentage is high; it has stopped continues growing. Moreover, in developing countries, although the prevalence of asthma is lower, it has a rising trend [6,7].

Migraine is a severe neurological disorder that can cause stroke and headaches, and may cause nausea, vomiting, and severe sensitivity to light and sound [8,9]. Migraine attacks can cause severe pain that persist for hours or days. Although, underlying factors and exact cause of migraine is unknown, however, they can related to the mix of genetic and environmental factors [10]. Generally, migraine accounts for 11% of the total adult population and creates a significant socio-economic burden on the community [11]. The prevalence of migraine in Europe and North America is the highest (13%) and in 9% reported in Asia [12]. Migraines are more common in women than men (ratio: 3:1) [13]; although, it is more common in boys than in girls before puberty [14].

Migraine and asthma both comprise inflammation and smooth muscle activation in the blood vessels or airway; thus, asthma-related inflammation may lead to a progression of migraine [15]. It is also possible that patients with asthma have excessive activated parasympathetic nerves that predispose them to migraine attacks [16]. Moreover, asthma does not directly trigger acute migraine, but environmental or genetic factors are commonly caused by the simultaneous onset of asthma and migraine attack [17].

However, evidence about the association and risk of migraine in patient with asthma and vice versa is somewhat confusing; thus, we conducted this meta-analysis to systematically assess the association and risk of migraine in patient with asthma and vice versa.

2. Methods

The protocol was registered in PROSPERO, an international prospective register of systematic reviews (Registration number: 42017072472). This systematic review was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [18] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19]. Ethical approval was not necessary for preparation of this article.

2.1. Search strategy

We systematically searched publishes articles indexed in PubMed, Scopus, Cochrane library, PsycINFO, CINAHL, ISI Web of Science, Science Direct from inception, and Embase databases until June 2017. Searched was performed using the following items: (asthma) and (migraine or headache or cephalgia or cephalalgia). Besides, to find more eligible evidences the reference lists of relevant publications were manually searched.

2.2. Inclusion criteria

Studies that fulfilled the following criteria, including observational studies (prospective cohort, retrospective cohort, case–control, or cross-sectional), the risk of migraine associated with asthma or vice versa that expressed as an adjusted hazard ratio (HR) or risk ratio (RR), as well as studies reported quantitative summaries on the relationship between asthma and migraine (e.g., odds ratios [ORs]), and those which full-text was accessible, were considered in the meta-analysis.

2.3. Exclusion criteria

Other article types include reviews (narrative or systematic), commentaries, letters to the editor, case series or case reports, and pooled analyses of original data were excluded. Besides, no language limitation was performed.

2.4. Data collection

Information was extracted using a data collection form, including first author name along with publication year, location, study design, sample size, demographic characteristics such as age and sex, criteria for enrolling, ascertainments of asthma, ascertainments and definitions of migraine, and disease of interest and comparison. Overall, two authors (F.R. and K.SH.) individually extracted the data of interest from studies. We contacted the authors of the eligible articles for missing data, if necessary.

2.5. Quality assessment

The quality assessment of the involved studies was done using the Newcastle-Ottawa Scale (NOS), including, comparability between groups, study group selection, and ascertainment of outcomes [20]. NOS scores of 7 or higher were considered as high quality. Any disagreements in the quality assessment findings were resolved with a third author (A.SM.) discussion.

2.6. Publication bias

To examine the potential for publication bias, visual inspection of funnel plots and the Egger test were used [21].

2.7. Statistical analysis

We combined the estimation of studies to investigate the relation between asthma and the subsequent development of

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migraine. We used the aggregate OR and RR with its 95% confidence interval (CI) to report the final pooled estimation. The I^2 statistic and Chi-square test of heterogeneity were used to assess the statistical heterogeneity among included studies. $I^2 > 50\%$ or $p < 0.05$ were considered to exhibit significant heterogeneity. Random effects method was used based on the results of heterogeneity test. In addition subgroup analysis was conducted according to population sample size (≥50,000 vs. <50,000), location (US vs. other countries) and socio-demographic characteristic such as sex and age. Review manager 5.3 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen) was used to provide pooled estimations, with corresponding 95% CI and plots.

3. Results

The search and study selection process is shown in Fig. 1. The organized search returned 2,005 unique references, of which 1532 were rejected through title and abstract and duplicated publication screening. Yielding 29 candidate abstracts, a subsequent full-text screening through eligibility phase rejected 24 studies, returning 11 candidates. Finally, 8 studies were reviewed and selected for data extraction [22,24–29]. Among the selected studies, 5 were reported the association between migraine with asthma risk (4 reported ORs and one study reported HRs in asthmatic vs. non-asthmatic patients, of which in the single study we calculated the OR following the contact and source data extraction) [22,26]. The rest three studies reported the risk of asthma in patient with migraine compared to non-moraine individuals (2 studies observed RR and a single study reported HR, of which in the single study we calculated the OR following the contact and source data extraction) [27,29]. Characteristics of included studies are given in Table 1. Eight studies with 389,573 unique individuals with age range between 5 and 80 years were included. The Newcastle-Ottawa Scale (NOS) for assessing the quality of both case–control and cohort studies with the scores ranged from 5 to 7, is show in Supplementary Table S1.

Of the studies, 2 were performed in USA [22,25], 3 in Europe [23,24,28], 2 in Taiwan [15,27], and 1 in UK [29]. Six studies were population based cohorts that selected participants from community-based population and two were case–control studies (Table 1). Of the included studies, 5 studies observed the association between migraine and asthma in patients with asthma vs. non-asthma cases [22,24–26], and 3 assessed the risk of asthma in migraine patient compared to non-migraine cases [27,29].

3.1. *The risk of migraine in asthma*

The OR of migraine for patient with asthma as compared with non-asthmatic individuals ranged from 1.44 (95% CI 1.02–2.06) to 2.01 (95% CI 1.24–3.26). In pooled estimates, the OR of migraine for patient with asthma as compared with non-asthmatic individuals was 1.62 (95% CI 1.43–1.82) (Fig. 2). Around 45% of the variability between studies' measures of association was due to the presence of heterogeneity (I^2 = 45%, $p < 0.00001$).

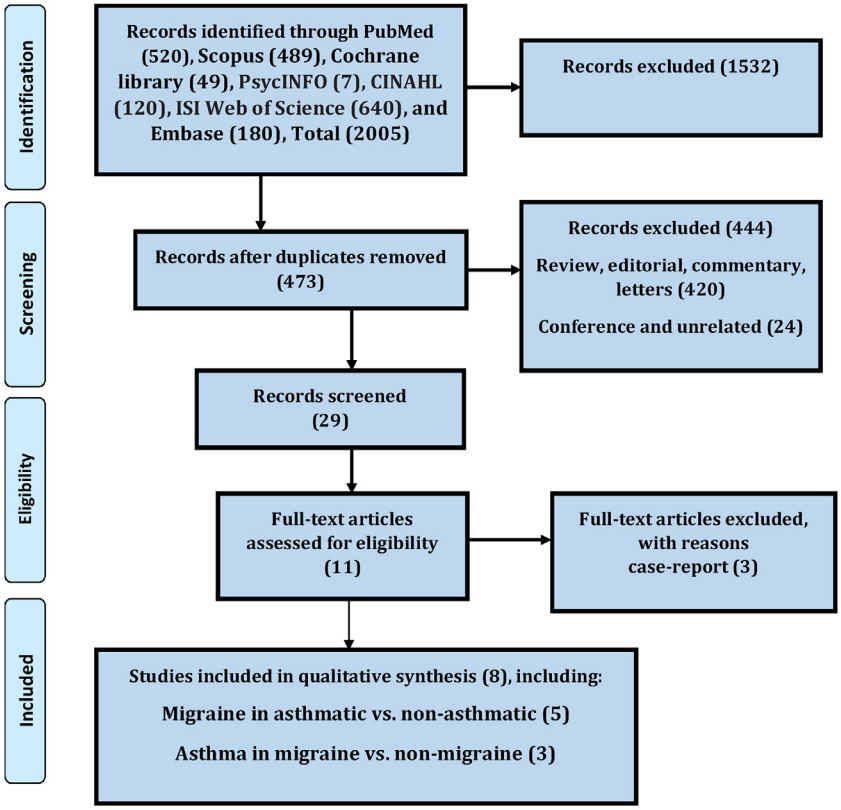

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of systematic literature review and article identification.

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Table 1 – Characteristics of the included studies.

Study ID	Country	Type of headache/ allergic	Methods			Participant				Findings
			Design	Size	Target group	Sex	Age (years)	Migraine OP	Asthma OP	
Migraine in asthma and non-asthma										
Wilkinson et al., 1994	Australia	Frequent headaches/ asthma and atopy or BHR	A prospective cohort study	925 (migraine)	Primary school children	F, M	5–12[b]	23%	20%	Asthma is independently related to migraine
Aamodt et al., 2007	Norway	Migraine/asthma	Head-HUNT cohort	51,383 (migraine)	Adult	F, M	51.1 (17.6)[a]	–	47.6%	Migraine are associated with asthma
Martin et al., 2016	USA	episodic migraine (EM)/ asthma	Observational cohort study	746 (asthma) 3700 (non-asthma)	Adults	F, M	50.0 (12.2)[a]	–	746 (16.8%)	Asthma is associated with an increased risk of migraine
Peng et al., 2016	Taiwan	Migraine/asthma	A nationwide cohort study	25,560 (asthma) 102,238 (non-asthma)	Adults	F, M	51.1 (19.6)[a]	–	25,560 (20%)	The risk of migraine in the asthmatic group was higher than that in the non-asthmatic group
Asthma in migraines and non-migraines										
Davey et al., 2002	UK	Migraine/asthma	Case–control study	64,678 (migraine)	Adults	F, M	30–50[b]	–	–	The raised risk of asthma in migraine patients
Becker et al., 2008	Sweden	Migraine/asthma	Case–control study	51,688 (migraine) 51,688 (non-migraine)	Adults	F, M	30–79[b]	–	16.8%	Migraine do not seem to be at an increased risk of developing asthma
Czerwinski et al., 2012	USA	Migraine/asthma	A prospective cohort study	671 (asthma) 3061 (non-asthma)	Adults	M	32.5 (4.6)[a]	–	13.1%	Found associations of migraine and asthma in a cohort
Peng et al., 2017	Taiwan	Migraine/asthma	A retrospective population-based cohort study	6647 (migraine) 26,588 (non-migraine)	Adults	F, M	40.1 (10.2)[a]	6647 (20%)	1128 (3.39%)	The risk of asthma risk was higher in migraine group than non-migraine group

OP, overall prevalence; BHR, bronchial hyper reactivity.
[a] Mean (SD) age.
[b] Age range.

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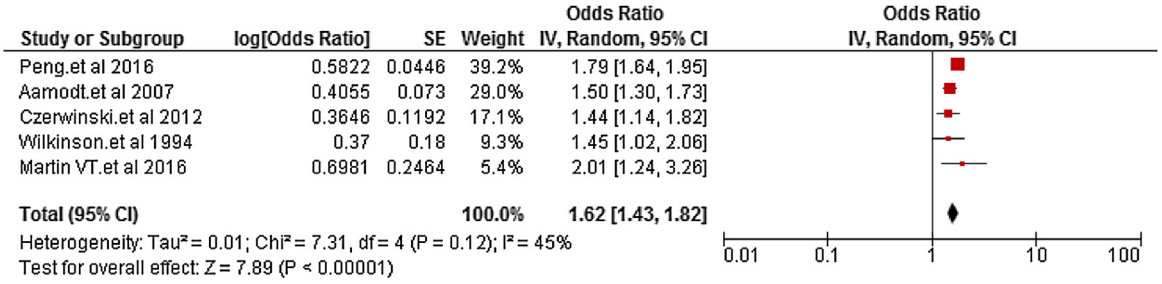

Fig. 2 – Pooled analysis for the association between migraine and asthma; CI, confidence interval; OR, odds ratio.

A sensitivity analysis was performed removing the study with the largest effect size from the OR summary analysis [22]. In this sensitivity analysis, OR for the remaining studies (OR 1.67; 95% CI 1.56–1.79) was pretty similar to the pooled OR for the complete studies.

3.2. *Migraine and risk of asthma*

Data pooling using a random-effect model showed that migraine was associated with a significant increased risk of asthma (RR: 1.56; 95% CI: 1.51–1.60; $p < .00001$) (Fig. 3). Around 94% of the variability between studies' measures of association was due to the presence of heterogeneity ($I^2 = 94\%$, $p < 0.00001$).

3.3. *Subgroup analysis*

In the subgroup analysis, studies were stratified by socio-demographic characteristic, location and sample size (Supplementary Figs. S1–S6).

As indicated in Table 2, two studies combined for the analysis of association between migraine and asthma in population more than 50,000. The pooled odds ratio (OR), was 1.65 (95%CI, 1.39–1.96) also in the population less than 50,000, the pooled estimation was 1.51 (95%CI, 1.26–1.81). The combined odds ratio of four studies with high heterogeneity (OR) was 1.40 (95%CI, 1.07–1.83), ($I^2 = 85\%$) for association between migraine and asthma after adjusting socio-demographic characteristic such as age and sex. Forest plot of subgroup analysis are in supplementary file. Two studies considering the relative risk (RR) of developing asthma in migraines compared with non-migraines was 1.06 (95%CI, 0.92–1.24) with high heterogeneity ($I^2 = 75\%$). The forest plot is shown in the supplementary file.

3.4. *Sensitivity analyses and publication bias*

The overall effect size by the OR pooled estimates did not significantly change and remained within the initial 95% CI when eliminated study one at a time; thus, no single study significantly affected the pooled OR. The funnel plot was visually symmetrical proposing that publication bias was not exist (Fig. 4A). In case of RR pooled estimates, the overall value

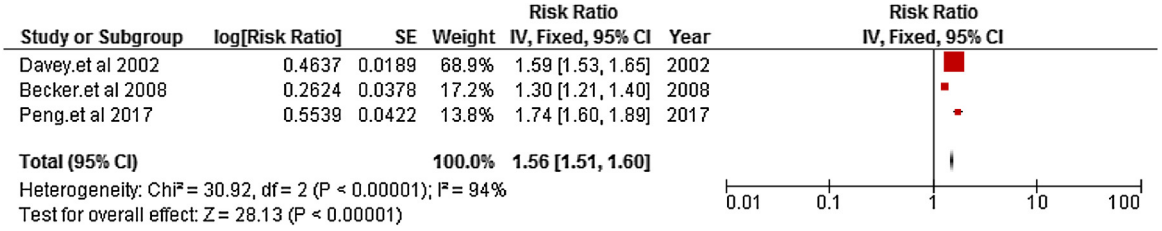

Fig. 3 – Pooled analysis for the association between migraine and asthma; CI, confidence interval; RR, relative risk.

Table 2 – Subgroup analysis for the association between migraine and asthma.

Subgroup	No. of patients	No. of study	I^2 (%)	Pooled estimate	
				OR (95% CI)	*p*
Sample size					
≥50,000	179,181	2	77	1.71 (1.58–1.84)	<0.001
<50,000	9121	3	0	1.51 (1.26–1.81)	<0.001
Location					
US	59,561	2	8	1.51 (1.21–1.87)	<0.001
Other countries	1001,943	3	60	1.69 (1.57–1.82)	<0.001
Socio-demographic[a]	149,394	4	64	1.69 (1.57–1.81)	<0.001

[a] Socio-demographic characteristic included variables such as sex and age.

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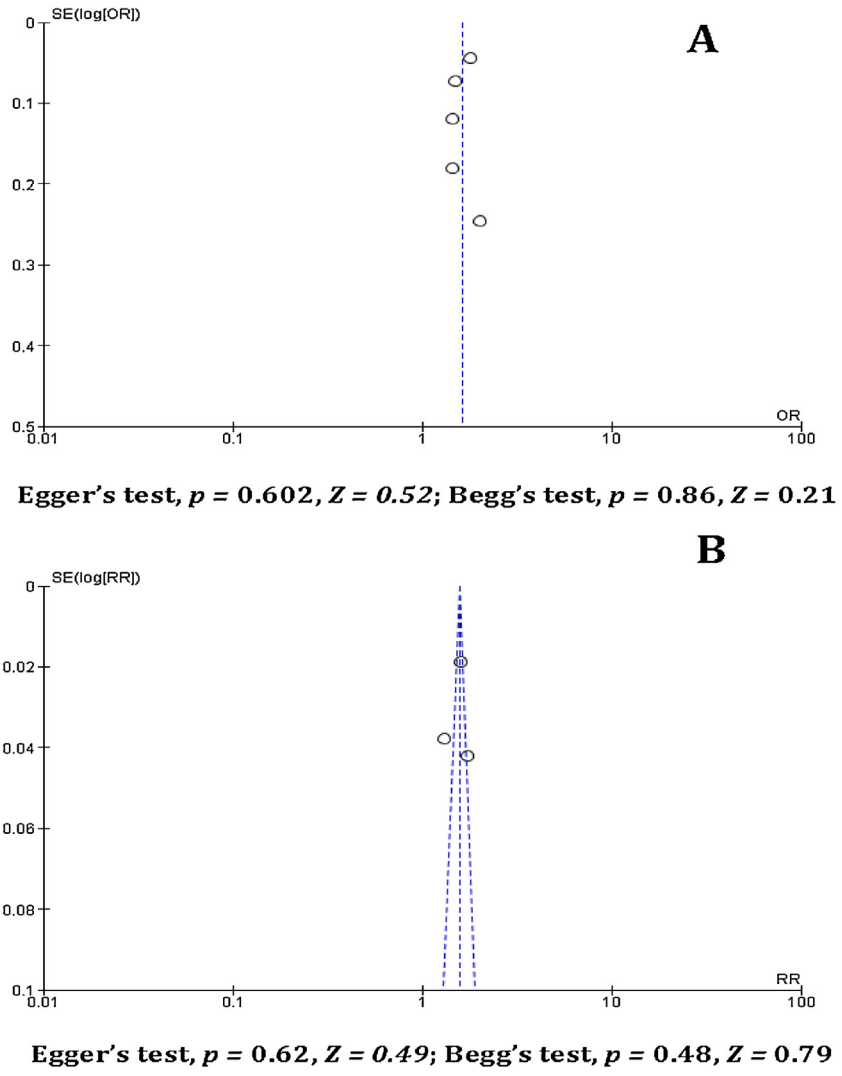

Fig. 4 – Funnel plot for the association between asthma and the risk of migraine (A), and migraine with the risk of asthma. CI, confidence interval.

fall within the initial 95%CI, and no single study affected the pooled RR significantly. The funnel plot was symmetrical revealing no publication bias (Fig. 4B).

4. Discussion

So far as we know, this is the first meta-analysis on the association between asthma and migraine, and the risk of asthma in patients with migraine as well. The present study pooling all existing studies shows that compared with individuals without migraine, those with migraine experience a 1.56-fold greater risk of asthma. Besides, the combined pooled effects demonstrated a 67% increased risk of asthma in those with migraine.

Consistent with our findings, previous conference report also exposed a positive association between migraine and the risk of asthma [30]. Previous studies also revealed that asthma is associated with an increased risk for transformations from episodic migraine to chronic migraine, which mean those patients experiencing the most severe respiratory symptoms are exposed to the greatest risk for such transformation [31,32].

Although possible mechanisms explaining this association remains yet undefined, we postulate several potential explanations. First both migraine and asthma are believed to implicate inflammatory and neuronal mechanisms [33]; furthermore, parasympathetic hyperactivity or mast cell degranulation, as associated with asthma [34] as well as shared genetic or environmental factors, might predispose a person to the imminent onset of chronic migraine [35,36].

A unidirectional underlying association between asthma and migraine is reasonable as a consequence of common biological mechanisms [37]. Atopy represents an example of such shared biological mechanisms, of which presents in 85% of patients with asthma [38]. This process is also revealed in the migraine cases and their association has reported so far [39,40]. The atopic theory may be consequent from the fact that involvement of allergen-specific IgE antibodies from plasma

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and mast cells upon exposure to an allergen, reported to both asthma and migraine cases [41]. Another possible common biological mechanism is a family of eicosanoid inflammatory mediators produced in leukocytes called Leukotriene. In asthma, leukotriene plays a major role, inflammatory mediators initiate the airway smooth muscle contraction and cause inflammation and airway hyper-responsiveness [42,43]. Besides, in migraine inflammation is present in form of both blood vessels constriction and dilation [44,45]. Leukotriene also plays a crucial role in the inflammatory response in headache, especially in migraine [46]; thus, inflammation could be the shared link between migraine and asthma [15].

So far researchers agree that better asthma control could ease migraines, as well though it has not confirmed that asthma attacks can prompt migraines, stressful patients with asthma may be more at risk of migraine [47], because stress is one of the important migraine provocateurs [48]. Even though when asthma happens, it makes an individual very anxious and uncomfortable, so once patients know how to control it, they can limit the stress and reduce the chance of migraine occurrence.

5. Conclusion

In conclusion, an important question is that dose a patient with asthma suffer from migraine or dose those who had migraine at risk of asthma? This is an area that has yet been neglected despite the connection between asthma and migraine in term of inflammatory and neuronal mechanisms, parasympathetic hyperactivity or mast cell degranulation, as well as shared genetic or environmental factors. Now it is unknown if control of the asthma will impact the severity of migraines or vice versa, but it is necessary to perform more research to further explain the mechanisms through which asthma increases the frequency of migraine or vice versa. If two conditions linked, once an individual undergo better control of asthma symptoms, might the excruciating migraine ease, too.

Author's contribution

Fakher Rahim, Arash Forouzan and Kiarash Shirbandi designed data collection tools, monitored data collection, wrote the statistical analysis plan, cleaned and analyzed the data, and drafted and revised the paper. Mehdi Sayyah, Amal Saki-Malehi and Fatemeh Javanmardi implemented the study, analyzed the data, and drafted. Fakher Rahim revised the paper.

Conflict of interest

None declared.

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None declared.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.pjnns.2018.07.004.

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Table 1: The Newcastle-Ottawa Scale (NOS) for assessing the quality of both case-control and cohort studies

Study	Selection				Comparability	Outcome			Total Quality score
Author, year	Representativeness of the exposed	Selection of the non-exposed	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability on the basis of the design or analysis controlled for confounders	Assessment of outcome	follow-up long enough for outcomes to occur	Adequacy of follow-up of	
Wilkinson et al, 1994	*	*	*	*	*	*	-----	-----	6
Davey, et al 2002	*	*	-----	*	-----	*	*	-----	5
Aamodt et al, 2007	*	*	*	*	*	*	-----	-----	6
Becker, et al 2008	*	*		*	*	*	*	*	7
Czerwinski et al, 2012	-----	-----	*	*	*	*	*	*	6
Vincent, et al 2015	*	*	*	-----	*	*	-----	-----	5
Peng, et al 2016	-----	-----	-----	*	*	*	*	*	5
Peng, et al 2017	*	*	-----	*	*	*	*	*	7