

Sensitization to common allergens among patients with allergy in major Iranian cities: A systemic review and meta-analysis

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Running title: Sensitization to common allergens in Iranian cities

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Abstract

Purpose: Various allergens are implicated in the pathogenesis of allergic diseases in different regions. This study attempted to identify the most common allergens among patients with allergy based on results of skin prick tests in different parts of Iran. **Methods:** Relevant studies were identified from the Medline database from 2000 to 2016. Six common groups of allergens including animals, cockroaches, foods, fungi, house dust mites and pollen were considered. Subgroup analysis was performed to determine prevalence of each type of allergens. Egger's test was used to assess publication bias. **Results:** We included 44 studies in this meta-analysis, the overall prevalence of positive skin tests to at least one allergen estimated 59% in patients with allergy in various parts of Iran. The number of patients was 11646 (56% male and 44% female) with mean age of 17.46 ± 11.12 years. most source of allergens were pollen 47%, mites 35.2% and food 15.3%. Prevalence of sensitization to food and cockroach allergens among children was more than adults. **Conclusion:** Pollens are the most common allergens in cities of Iran with warm and dry climate, however, sensitization to house dust mites is predominant in northern and southern coastal areas of Iran.

Key words: Allergens, Cockroach, Fungi, Pollen, Sensitization, Iran

Introduction

The term allergen is used to describe any substance therein capable of stimulating production of immunoglobulin E (IgE) in a genetically predisposed individual (1). The first allergens were identified in 1980s. So far, a lot of allergens have been reported by cross- referencing databases such as Allergome and Pfam data (2,3). The most clinically important allergens are related to animals, cockroaches, house dust mites (HDM), foods, fungi, pollens, latex and venom. Outdoors sources are likely to be pollens, and HDMs are more common indoor allergens (4).

Most of animal allergens belong to mammals and birds which are easily spread into the environment (5-7). Sensitization to cockroaches is among the most common factors for increasing asthma morbidity. It appears genetic background may play a role in susceptibility to cockroach sensitization, too (8,9). HDMs are an important factor for exacerbating different types of allergic

diseases in predisposed individuals. These small arthropods can live in close contact with humans and are found in large numbers in beds, sofas, carpets and furniture. The growing of mites decreased in environments with low humidity and extreme temperatures (10, 11). Food allergic patients, mainly children, show a higher sensitization to ingestion of egg, cow's milk, nuts, soy, sea foods and wheat. However, allergy to various fruits and vegetables are also reported with lower frequencies(12,13). Fungi are primarily considered outdoor allergens but *Aspergillus* species can be found inside the warm and humid places (14,15). Pollen allergens arise from pollination processes occurring by tree, weed and grass. In many regions around the world, trees compromise the clinically most relevant sources of allergenic pollens. Weeds can be defined as unwanted plants, and grasses are ubiquitous plants which over 95% of allergy (16-18).

As a diagnostic test, skin prick test (SPT) is routinely used to detect IgE-mediated sensitization to specific allergens. SPT were performed using standard commercial extracts of allergens with a sterile lancet on the forearms. The results of the skin tests were examined after 15 min and considered positive when the wheal was 3 mm greater in diameter than the negative control (saline) (19).

Iran as the second largest country in Middle East and 18 th- largest in the world has a total area 1,648,195 km² and a population of around 78.4 million (in 2016). Iran has a hot and dry climate in most areas but there is high humidity on the northern coastal area of the Caspian Sea and southern coastal area of the Persian Gulf. Iran is divided into thirty one provinces. As shown in figure 1, Tehran (Karaj was a part of it), Mashhad, Isfahan, Tabriz, Shiraz and Ahvaz are the five biggest cities.

This systematic review and meta- analysis was designed to determine the prevalence of sensitization to common allergens using the published data in different regions of Iran.

Materials and Methods

Search method

The literature and reference search were performed in March 2016. The present study was designed based on the guide-lines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (20). Persian and English data bases were searched from January 2000 to March 2016. The Medline database such as Iranian (Magiran, Iran Medex) and

international databases (PubMed, ProQuest, Scopus SID, Google Scholar and Science Direct) were identified.

The articles were searched based on the keywords ("Allergens"[Mesh]) AND "Iran"[Mesh], ("Asthma"[Mesh]) AND "Iran"[Mesh] "Allergic rhinitis" AND "Iran" AND "Atopic dermatitis" and "Iran" AND "skin test" AND "Iran". The references of all included studies were also used to find the additional papers.

Data extraction

To assessing of the inclusion criteria, two authors (MM and SHT) separately screened the title, abstract and then reviewed the full texts of studies. The percent agreement of two authors was obtained 93% which showed a high agreement between authors. Any disagreements were resolved by consultation with a third author (SF) for final decision.

To assess quality of studies included in met-analysis, we selected six items of STROB checklist included: 1-Clearly defined the outcome, i.e., Allergen. 2-Gave the eligibility criteria. 3-Presented key elements of study design. 4- Reported numbers of outcome events. 5- Explained how the study sample was arrived at. 6- Described the setting, locations, and relevant dates. The studies that fulfilled all criteria were classified as high quality. The studies that did not meet one criterion were classified as intermediate quality and the studies that did not fulfill more than one criterion were classified as low quality.

We extracted information such as the name of first author, publication year of article, province which study was perform, type of study, sample size of study, age and sex of patients. The rate of sensitization to at least one of allergens including animal, cockroach, food, fungi, HDM and pollen was reported, too.

Inclusion and exclusion criteria

Studies were included in this meta-analysis if these criteria were met for them: 1) study was conducted between January 2000 to March 2016; 2) provided sufficient information to estimate prevalence of allergen and its Standard Error (SE) and Confidence Interval(CI); 3) descriptive statistics of age and sex and prevalence of at least one of allergens in term of types of characteristics such as animal, cockroach, food, fungi, HDM and Pollen was reported; 4) Only cross-sectional studies included in this meta-analysis; 5) Papers were published in Persian or

English language;6) Studies in which participants had a primary diagnosis for allergy including asthma, allergic rhinitis, atopic dermatitis, food allergy, chronic sinusitis and chronic urticaria

Studies were excluded, if: 1) studies such as randomized controlled trials, case report studies and animal studies; 2) articles which did not offer enough data to calculate the estimate prevalence of allergen; 3) studies in which venom allergens and latex allergens reported (they were used in discussion); 4) overlapping articles

Statistical analysis

We present the effect size for each study as prevalence (p). Standard error (SE) of each study was calculated based on binomial distribution. The results for each study and pooled outcome revealed as a forest plot [reported as Effect Estimates (ES) with the 95% confidence interval (95% CI)]. To assess heterogeneity among studies beside the I-square statistic (I^2) (25%, “Low”; 50% , “medium” and 75% as “high” heterogeneity) Cochran's Q test ($P < 0.1$ was statistically significant) also reported. Subgroup meta-analysis was used to compare the prevalence of allergens based on the results of SPT and different ages. Egger's test was used to evaluate the publication bias which plots the regression line between precision of the studies (independent variable) and the standardized effect (dependent variable). Stata statistical software (Chicago, IL, USA, version 11) was used to data analyses.

Results

Literature Search

Initial database searches identified 352 articles and an additional 6 studies through hand searches and expert suggestions, giving a total of 358 articles that were screened. Out of these, 156 were chosen for reading of full text and 44 were included in this meta- analysis. Figure 2 shows our article selection according to the PRISMA flowchart.

Characteristics of Studies

All studies reported in this systematic review and meta-analysis performed as cross-sectional study. Finally, 44 studies which contained 11646 patients (56% male and 44% female) had been included in this meta-analysis (21-64). The mean of patients' age was 17.7 (95% CI: 14.0, 21.4)

years. Of the 44 selected research studies, 15 examined animal allergens, 17 cockroach allergen, 21 food allergens, 23 fungal allergens, 25 HDM allergen and 22 pollen allergens. The basic characteristics of published studies were presented in table1.

Prevalence of various animal allergens among patients with allergy has shown in Figure 3. These patients were most commonly sensitized to animal dander (33%). And the other types of animal allergens showed close prevalence rate (about 18%).

Sensitivity to food allergens has shown in Figure 4. Positive skin test for cow's milk, egg and nuts was obtained 16%, 18% and 15% , respectively. Also, overall sensitization to food allergens was 15%.

As shown in Figure 5, the common fungi allergen was candida(27%) followed by cladosporium(26%), alternaria(20%) and aspergillus(17%).

Sensitization to HDMs is 33% that has shown in Figure 6. There is no significant differences between the prevalence of *Dermatophagoides pteronyssinus* and *Dermatophagoides farina* in patients with allergy.

As shown in Figure 7, overall sensitization to pollen allergens was 45% in patients with allergy. Wood with the highest prevalence (54%), followed by grass (55%) and tree (40%) had more prevalence, respectively.

According to results of subgroup analysis, estimate frequency of common allergens in major cities of Iran has shown in Table 2. The highest sensitization to animal allergens and HDMs has been detected in coastal cities. The highest prevalence of cockroach was reported to be in Shiraz and Ahvaz. Sensitization to different food allergens was approximately the same. The highest prevalence rate of fungi allergen was in Tehran. The highest frequency of sensitization to pollens was in Ahvaz, Mashhad and Shiraz in order (Table2).

The age distribution of patients with allergy to common allergens is given in Table 3. Cockroach allergens were more prevalent in children ≤ 16 years than adults. Prevalence of sensitization to food allergens were also significantly higher in patients younger than 5 years compare with older age, 26.2% (95% CI : 22.8% -29.7%). But prevalence of sensitization to other allergen such as animal, fungi, HDM and pollen had more prevalence among adult (Table3).

The results of Egger's test for each of subgroup allergens showed there was no publication bias among the studies ($P>0.05$) (Table 4).

Discussion

Allergy is defined as an allergen- specific hypersensitivity disease. We estimated the prevalence of six common types of allergens including animals, cockroaches, foods, fungi, HDMs and pollens in patients with allergy in major cities of Iran. This study estimated the prevalence of sensitization to at least one of allergens is 59% of the allergic patients according to the results of SPT. However, because of the insufficiency of data in some cities such as Isfahan, we could not show the meticulous prevalence of sensitization to allergens in Iran. Furthermore, all patients in these selected studies were not tested with all the considered allergens.

Our study demonstrated that the prevalence of positive SPT was generally consistent with most neighboring countries. An analysis of SPT reactions in patients with allergic rhinitis in Turkey yielded a positive result of 61% (65), in Pakistani 69% (66) and in Riyadh 75%(67). A large difference was observed in positive SPT in Russian patients with 21.8% (68).

Keeping dog at home and direct exposure to this animal is very much limited in Iran because religious believes; however, sensitization to animal allergens (cat, dog and feather mix) was about 20% among allergic patients. Direct contact to animals is a way for sensitization but animal allergens can be transferred to environments that were never occupied by the animals (69).Animal hypersensitivity was detected in 26% of Turkish patients with allergy where there is low pet ownership rate similar to Iran (70). In the current study the highest prevalence of sensitization to animal allergens was in coastal areas. This difference can be explained by performing SPT with animal dander extract including a broader type of animal allergens in study of Bushehr (35).

Overall sensitization to cockroach was 25% among Iranian patients with allergy. The prevalence of cockroach sensitization was reported to be 12% in 337 tested children in Turkey (71), 33% in 151 asthmatic patients in Saudi Arabia (72) and 68.4% in asthmatic patients in Russia (73).It seems that sensitization to cockroach is more common among patients with asthma than in other cases of allergy. Positive reaction to cockroach was the highest in allergic patients living in Ahvaz and Shiraz; it might be explained by the high level of cockroach infestation due to warm climate in southern Iran. The children had higher positive sensitization to cockroach, therefore, application of insecticides and vigorous children's bedroom cleaning can be accomplished by decreasing sensitization in them.

Our included studies showed that according to SPT, sensitization to food allergens was overall 15% in patients with allergy. Sensitization to food allergens is the highest in Australia (83%) and the UK (74%). The reason of lower incidence of food sensitization in Iranians may be their various genetic backgrounds. Lower prevalence of food sensitization among adults than infants can be because of occurring natural tolerance during the increasing age(75). The most common food sensitizations were egg (18%), cow's milk (16%) followed by nut (15%) and wheat (8%), this frequency is according to other studies (76, 77). It is noticeable that the specificity of SPT is generally low for food allergen, partly because of enzymatic degradation of food proteins through preparation of extracts as well as cross reactions between some food groups (19). Saffron a spice which is mostly cultivated in Iran, Varasteh et al. showed positive immediate skin reaction to saffron in 70% of the patients (64). There is no significant difference for sensitization to food allergens in major cities of Iran.

The prevalence of sensitization to numerous fungal allergens was reported from 5% to 20% in Iranian patients with allergy (78). There are two reports on the prevalence of allergy to candida in Iran, one was in patients with rhinitis with 0.7% in Shiraz and the other in patients with eczema and asthma with 53% in Tehran (41,44). Candida is a commensal normal flora of the skin, gastrointestinal and genitourinary tracts although the significance of candida in allergy is still controversial in the literature (79); meanwhile, cross- reactivity of fungal allergens should be considered (80). Sensitization to other fungal allergens including Cladosporium, Alternaria, Aspergillus and Penicillium was the highest in Tehran and coastal areas because of the climate conditions.

Sensitization to HDM allergens in Iranian patients with allergy was 33% in this study. Positive sensitization in neighboring countries was reported from 25% in Turkish (81), 46% in United Arab Emirates (82) and 67% in Russia (83). Sensitization to mites in patients with allergy live at sea level was higher than those live in the high altitude areas in Iran because mites grow better in higher humidity (84).

In Iranian patients, the most common sensitization was to pollens from weed, grass and tree allergen (45%) in all cities except coastal areas. Recent studies have shown the impact of climate change on aeroallergens acculturation, as global warming increases the pollen production by

plants, allergenicity of pollens, increase in production period and distribution of pollens, and changes in plant biomass (85,86). The results of subgroup analysis showed that the prevalence of sensitization to pollens was higher in Southwestern Iran including Ahwaz and Shiraz than the other regions of Iran. Southwest of Iran has a dry and hot climate with a short winter, it causes increase in production period and distribution of pollens. In recent years, the effects of Middle East storms have become a problematic phenomenon on allergic diseases in southern provinces of Iran (87).

There are the other allergens from the many diverse sources associated with allergic disease. Latex products are occupational- associated aeroallergens that clinical significance of this allergen varies according to patient subgroups. Sensitization to latex allergen in Iran was reported from 18% to 38% in health care personnel (88-90), and no sensitization observed in workers in latex glove factories (91).

There is no report of the prevalence of insect-sting allergies and its mortality in Iran. Bemanian et al. suggested a relatively fast and safe protocol of venom immunotherapy in ten patients with systemic reaction to honeybee or yellow jacket bee (92).

No significant publication bias was seen among published studies; it seems that both studies with low prevalence and high prevalence were participated in this meta-analysis.

A positive skin test is not enough to confirm the presence of allergic disease, however; it shows allergic sensitization which need to evaluation of clinical symptoms and it also may predict the subsequent onset of allergic symptoms (86). The differences in the age range of people who were enrolled in different studies could be introduced as one of the source of heterogeneity among allergens. There was not enough published data for considering of poly-sensitization to diverse allergens.

Conclusion

The results of this study estimated the prevalence of sensitization to at least one of considered allergens was 59% based on the results of SPT. In most parts of Iran with dry and hot climate, pollens were the most types of allergens and sensitization to mites in northern and southern coastal areas of Iran was the most common. This study will help for selecting the panel of most

common allergens for SPT and will also help in finding the best species of allergens for immunotherapy in this area.

References

1. Mari A. When does a protein become an allergen? Searching for a dynamic definition based on most advanced technology tools. *Clin Exp Allergy*. 2008 Jul;38(7):1089-94.
2. Bergmann KC, Ring J. History of allergy. *Pediatric Allergy and Immunology*. 2014 Oct; 25(6):i. doi: 10.1111/pai.12292
3. Radauer C, Bublin M, Wagner S, Mari A, Breiteneder H. Allergens are distributed into few protein families and possess a restricted number of biochemical functions. *J Allergy Clin Immunol*. 2008 Apr;121(4):847-52.e7.
4. Ring J1, Akdis C, Behrendt H, Lauener RP, Schäppi G, Akdis M, Ammann W, de Beaumont O. et al. Davos declaration: allergy as a global problem. *Allergy*. 2012 Feb;67(2):141-3.
5. Chapman MD, Wood RA. The role and remediation of animal allergens in allergic diseases. *J Allergy Clin Immunol* 2001; 107:S414-421.
6. Zahradnik E, Raulf M. Animal allergens and their presence in the environment. *Front Immunol* 2014; 5:76.
7. Moghtaderi M, Farjadian S, Abbaszadeh Hasiri M. Animal allergen sensitization in veterinarians and laboratory animal workers. *Occup Med (Lond)* 2014; 64:516-520.
8. Do DC, Zhao Y, Gao P. Cockroach allergen exposure and risk of asthma. *Allergy*. 2016 Apr;71(4):463-74.
9. Moghtaderi M, Farjadian S, Fereidouni M, Nasiri M, Nejat Indoor Dust Allergen Levels in the Homes of Patients with Childhood Asthma: An Experience From Southwestern Iran. *Iran J Allergy Asthma Immunol*. 2016 Apr;15(2):132-7.
10. Patel S, Meher BR. A review on emerging frontiers of house dust mite and cockroach allergy research. *Allergol Immunopathol (Madr)*. 2016 Mar 16. pii: S0301-0546(16)00004-5. doi: 10.1016/j.aller.2015.11.001.

11. Peat JK, Tovey E, Toelle BG, Haby MM, Gray EJ, Mahmic A, et al. House dust mite allergens. A major risk factor for childhood asthma in Australia. *Am J Respir Crit Care Med* 1996; 153(1):141-6.
12. Allen KJ, Koplin JJ. The epidemiology of IgE-mediated food allergy and anaphylaxis. *Immunol Allergy Clin North Am*. 2012 Feb;32(1):35-50.
13. Hassan AK, Venkatesh YP. An overview of fruit allergy and the causative allergens. *Eur Ann Allergy Clin Immunol*. 2015 Nov;47(6):180-7.
14. Fukutomi Y, Taniguchi M. Sensitization to fungal allergens: Resolved and unresolved issues. *Allergol Int*. 2015 Oct;64(4):321-31.
15. Vermani M, Vijayan VK, Agarwal MK. Identification of *Aspergillus* (*A. flavus* and *A. niger*) Allergens and Heterogeneity of Allergic Patients' IgE Response. *Iran J Allergy Asthma Immunol*. 2015 Aug;14(4):361-9.
16. Mothes N, Valenta R. Biology of tree pollen allergens. *Curr Allergy Asthma Rep*. 2004 Sep;4(5):384-90.
17. Stemeseder T, Hemmer W, Hawranek T, Gadermaier G. Marker allergens of weed pollen - basic considerations and diagnostic benefits in the clinical routine: Part 16 of the Series Molecular Allergology. *Allergo J Int*. 2014;23(8):274-280. Epub 2014 Dec 23.
18. Andersson K, Lidholm J. Characteristics and immunobiology of grass pollen allergens. *Int Arch Allergy Immunol*. 2003 Feb;130(2):87-107.
19. Chiriac AM, Bousquet J, Demoly P. In vivo methods for the study and diagnosis of allergy. *Middleton's Allergy Principles and Practice*. 8th ed. Philadelphia: Mosby Elsevier; 2013. p. 1119-29.
20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; 339: b2535.
21. Abdollahi-Fakhim S, Sadegi-Shabestari M, Mousavi-Agdas M, Naghavi-Behzad M, Alikhah H. Medical treatment of allergy in children with recurrent or chronic sinusitis. *Nigerian Medical Journal : Journal of the Nigeria Medical Association*. 2014;55(6):474-479.

22. Ahanchian H, Jafari S, Behmanesh F, Haghi NM, Nakhaei AA, Kiani MA, Radbin MH, Kianifar H. Epidemiological survey of pediatric food allergy in Mashhad in Northeast Iran. *Electron Physician*. 2016 Jan 15;8(1):1727-32.
23. Ahmadiafshar A, Sepehri S, Moosavinasan SN, Torabi SZ. Recognition and frequency determination of common allergens in allergic patients of Zanjan city by skin prick test. *ZUMS Journal* 16 (64), 47-56.
24. Akbari H, Rezaei A. Common allergens for allergic patients in Isfahan: A clinically-based study. *Journal of Research in Medical Sciences*. 2000 Mar 5.
25. Mokhtari Amirmajdi M, Mokhtari Amirmajdi NA, Eftekharzadeh Mashhadi I, Jabari Azad F, Tavakol Afshari J, Shakeri MT. *Alternaria* in patients with allergic rhinitis. *Iran J Allergy Asthma Immunol*. 2011 Sep;10(3):221-6.
26. Arshi S, Zarrinfard R, Poorsattar A, Fereshtehnejad SM, Javahertarash N. Prick test: a survey and comparison between Iranian allergic children and adults. *Allergol Immunopathol (Madr)*. 2010 Sep-Oct;38(5):287-90.
27. Assarehzadegan MA, Shakurnia A, Amini A. The most common aeroallergens in a tropical region in Southwestern Iran. *World Allergy Organ J*. 2013 Apr 4;6(1):7.
28. Behmanesh F, Shoja M, Khajedaluae M. Prevalence of Aeroallergens in Childhood Asthma in Mashhad. *Macedonian Journal of Medical Sciences*. 2010 Sep 15; 3(3):295-298.
29. Bermanian MH, Alizadeh Korkinejad N, Shirkhoda S, Nabavi M, Pourpak Z. Assessment of sensitization to insect aeroallergens among patients with allergic rhinitis in Yazd City, Iran. *Iran J Allergy Asthma Immunol*. 2012 Sep;11(3):253-8.
30. Bonyadi MR, Azarshin N, Baybordi B, Elmiye A. Frequency of Mold Allergens in Allergic Rhinitis Patients. *MLJ*. 2014; 8(1):77-81.
31. Saeedeh Farajzadeh S, Bazargan N, Shahesmaeili A, Gholami Shahrabaki A, Fekri AR. Evaluation of the Frequency of Food Allergens by Skin Prick Test in Children with Atopic Dermatitis. *Iranian Journal of Dermatology* 2010; 13(2): 33-36.

32. Farhoudi A, Pourpak Z, M. Mesdaghi M. Chavoshzadeh Z, Kazemnejad A. The Study of Cockroach Allergy in Iranian Children with Asthma. *IJMS*. 2002 Dec; 27(4): 156-160.
33. Farhoudi A, Razavi A, Chavoshzadeh Z, Heidarzadeh M, Bermanian MH, Nabavi M. Descriptive study of 226 patients with allergic rhinitis and asthma in karaj city. *Iran J Allergy Asthma Immunol*. 2005 Jun;4(2):99-101.
34. Farjadian S, Moghtaderi M, Kashef S, Alyasin S. Sensitization to food allergens in Iranian children with mild to moderate persistent asthma. *World J Pediatr*. 2012 Nov;8(4):317-20.
35. Farrokhi S, Gheybi MK, Movahed A, Tahmasebi R, Iranpour D, Fatemi A, Etemadan R, Gooya M, Zandi S, Ashourinejad H, Alavizadeh S, Khoddami S. Common aeroallergens in patients with asthma and allergic rhinitis living in southwestern part of Iran: based on skin prick test reactivity. *Iran J Allergy Asthma Immunol*. 2015 Apr;14(2):133-8.
36. Fazlollahi MR, Pourpak Z, Yeganeh M, Kardor GH, Kazemnejad A, Movahedi M, Gharagozlow M, Farid Hosseini R, Farhoudi A. Sesame seed allergy: Clinical manifestations and laboratory investigations. *Tehran University Medical Journal* 2007 Nov;65 (8):85-90
37. Fereidouni M, Hossini RF, Azad FJ, Assarehzadegan MA, Varasteh A. Skin prick test reactivity to common aeroallergens among allergic rhinitis patients in Iran. *Allergol Immunopathol (Madr)*. 2009 Mar-Apr;37(2):73-9.
38. Fouladseresht H, Safiri S, Moghadas Amiri M, Razeghi M, Bazargan N. The prevalence of food and inhalational allergens in allergic patients in Kerman. *J Kermanshah Univ Med Sci*. 2014;18(4):234-241.
39. Ghaffari J. Prevalence of Aeroallergens in Skin Test of Asthma, Allergic Rhinitis, Eczema and Chronic Urticaria Patients in Iran. *J Mazand Univ Med Sci* 2012; 22(87): 139-151.
40. Hosseini S, Shoormasti RS, Akramian R, Movahedi M, Gharagozlou M, Foroughi N, Saboury B, Kazemnejad A, Mahlooji Rad M, Mahdavian A, Pourpak Z, Moin M. Skin Prick Test Reactivity to Common Aero and Food Allergens among Children with Allergy. *Iran J Med Sci*. 2014 Jan;39(1):29-35.
41. Kashef S, Kashef MA, Eghtedari F. Prevalence of aeroallergens in allergic rhinitis in shiraz. *Iran J Allergy Asthma Immunol*. 2003 Dec;2(4):185-8.

42. Khazaei HA, Hashemi SR, Aghamohammadi A, Farhoudi F, Rezaei N. The study of type 1 allergy prevalence among people of South-East of Iran by skin prick test using common allergens. *Iran J Allergy Asthma Immunol*. 2003 Sep;2(3):165-8.
43. Khazaei HA, Khazaei B, Dashtizadeh GA, Mohammadi M. Cigarette Smoking and Skin Prick Test in Patients With Allergic Rhinitis. *Int J High Risk Behav Addict*. 2015 Sep 1;4(3):e23483.
44. Khosravi AR, Bandghorai AN, Moazzeni M, Shokri H, Mansouri P, Mahmoudi M. Evaluation of *Candida albicans* allergens reactive with specific IgE in asthma and atopic eczema patients. *Mycoses*. 2009 Jul;52(4):326-33.
45. Mahram M, Barikani A, Nejatian N. The Frequency of Common Allergens in Allergic Rhinitis among the Patients Referred to the Allergy Clinic of Qods Hospital in Qazvin during 2007-2010. 2013 *J Aller Ther* 4 (1):130.
46. Moghtaderi M, Aleyasin S, Amin R, Kashef S. Skin test reactivity to fungal aeroallergens in asthmatic children in southern Iran. *Iran J Pediatr*. 2010 Jun;20(2):242-3.
47. Moghtaderi M, Farjadian S, Kashef S, Alyasin S, Afrasiabi M, Orooj M. Specific IgE to common food allergens in children with atopic dermatitis. *Iran J Immunol*. 2012 Mar;9(1):32-8.
48. Moghtaderi M, Farjadian S, Reihani I. Sensitization to plant food allergens in patients with asthma. *Indian J Allergy Asthma Immunol* 2015;29:24-7.
49. Moghtaderi M, Hejrati Z, Kolahi N, Heidari B. Sensitization to aeroallergens in patients with allergic rhinitis, asthma, and atopic dermatitis in Shiraz, Southwestern Iran. *Indian J Allergy Asthma Immunol* 2015;29:79-83.
50. Moghtaderi M, Farjadian S, Hosseini Z, Eghtedari D. The comparison of sensitization to animal allergens in children and adult-onset patients with asthma. *Indian J Allergy Asthma Immunol* 2015;29:67-71.
51. Mohammadi K, Gharagozlou M, Movahedi M. A single center study of clinical and paraclinical aspects in Iranian patients with allergic rhinitis. *Iran J Allergy Asthma Immunol*. 2008 Sep;7(3):163-7.

52. Mohammadzadeh I, Ranjbar B, Alizadeh Navaei R, Aziznejad P. Mite Sensitivity in Children with Allergy. *J Babol Univ Med Sci* Jul 2012; 14(4): 78-82.
53. Movahedi M, Moin M, Farhoudi A. A comparison between diagnostic clinical tests and herbal geography in allergic patients in Tehran and Karaj cities. *Iran J Allergy Asthma Immunol*. 2000;1(1):29-31.
54. Nabavi M, Hoseinzadeh Y, Ghorbani R, Nabavi M. Prevalence of food allergy in asthmatic children under 18 years of age in Semnan-Iran in 2007-2008. *koomesh*. 2010; 11 (3) :162-168.
55. Nabavi M, Ghorbani R, Farzam V. Prevalence of Mold Allergy in Asthmatic Patients of Less than 18 Years Old in Semnan. *Journal of Kerman University of Medical Sciences*, 2010; 17(4): 328-336.
56. Nabavizadeh S, Yazdanpanah S, Abidi H, Zoladl M. The incidence of Common Allergens in Patients with Allergic Rhinitis Referred to Shahid Mofatteh Clinic, Yasuj, Iran. *Armaghane danesh*. 2013; 18 (9) :736-745
57. Onsoni F, Ahmadi A, Mansoori M, Mousavi SM, Pazooki N, Salimian J. The prevalence of food allergens in patients with atopic dermatitis in Tehran in 2014. *Scientific Journal of Kurdistan University of Medical Sciences*. 2016; 21:40-46.
58. Pourpak Z, Farhoudi A, Arshi S, Movahedi M, Gharegozlou M, Yazdani F, Mesdaghi M. Common Food Allergens in Iranian Children. *IJMS* Mar 2003;28(1):17-22.
59. Pourpak Z, Farhoudi A, Mahmoudi M, Movahedi M, Ghargozlou M, Kazemnejad A, Eslamnoor B. The role of cow milk allergy in increasing the severity of atopic dermatitis. *Immunol Invest*. 2004 Feb;33(1):69-79.
60. Safari M, Amin R, Kashef S, Aleyasin S, Ayatollahi M. Cockroach Sensitivity in Iranian Asthmatic Children under the Age of Five years. *Tur Toraks Der* 2009;10:26-30.
61. Salehi T, Pourpak Z, Karkon S, Shoormasti RS, Sabzevari SK, Movahedi M, Gharagozlou M, Moin M. The study of egg allergy in children with atopic dermatitis. The study of egg allergy in children with atopic dermatitis.

- 62 . Shakurnia AH, Assarehzadegan MA, Mozaffari AR, khodadadi A, Amini A, Shakerinejad Gh, Maneshdavi N. Prevalence of aeroallergens sensitivity in asthmatic patients from Ahvaz. *Jentashapir J Health Res* 2014;5(1):461-468.
63. Shakurnia AH, Assarehzadegan MA, Mozaffari AR, Shakerinejad Gh, Amini A. Mite and Cockroach Allergy in Patients with Respiratory Allergies A Report from Ahvaz. *Medical Journal of Tabriz University of Medical Sciences and Health Services* 2013; 35(2): 50-55.
64. Varasteh AR, Vahedi F, Sankian M, Kaghazian H, Tavallaie S, Abolhassani A, Kermani T, Mahmoudi M. Specific IgG antibodies (total and subclasses) against Saffron pollen: a study of their correlation with specific IgE and immediate skin reactions. *Iran J Allergy Asthma Immunol.* 2007 Dec;6(4):189-95.
65. Aydin S, Hardal U, Atli H. An analysis of skin prick test reactions in allergic rhinitis patients in Istanbul, Turkey. *Asian Pac J Allergy Immunol.* 2009 Mar;27(1):19-25.
66. Ahmed A, Minhas K, Micheal S, Ahmad F. Prevalence of skin test reactivity to aeroallergens in the Pakistani population. *Public Health.* 2011 May;125(5):324-6.
67. Almogren A. Airway allergy and skin reactivity to aeroallergens in Riyadh. *Saudi Med J.* 2009 Mar;30(3):392-6.
68. Vartiainen E, Pet äys T, Haahtela T, Jousilahti P, Pekkanen J. Allergic diseases, skin prick test responses, and IgE levels in North Karelia, Finland, and the Republic of Karelia, Russia. *J Allergy Clin Immunol.* 2002 Apr;109(4):643-8.
69. Zahradnik E, Raulf M. Animal allergens and their presence in the environment. *Front Immunol* 2014; 5:76.
70. Mungan D1, Celik G, Bavbek S, Misirligil Z. Pet allergy: how important for Turkey where there is a low pet ownership rate. *Allergy Asthma Proc.* 2003 Mar-Apr;24(2):137-42.
71. Yilmaz A, Tuncer A, Sekerel BE, Adalioğlu G, Saraçlar Y. Cockroach allergy in a group of Turkish children with respiratory allergies. *Turk J Pediatr.* 2004 Oct-Dec;46(4):344-9.
72. Koshak EA. Skin test reactivity to indoor allergens correlates with asthma severity in jeddah, saudi arabia. *Allergy Asthma Clin Immunol.* 2006 Mar 15;2(1):11-9.

73. Berzhets BM, Petrova NS, Barashkina OF, Efremenko II, Dotsenko EA, Prishchepa IM. [Role of cockroaches *Blatella germanica* in the development of atopic bronchial asthma]. Zh Mikrobiol Epidemiol Immunobiol. 2001 Jul-Aug;(4):43-6.
74. de Benedictis FM, Franceschini F, Hill D, Naspitz C, Simons FE, Wahn U, et al. EPAAC Study Group. The allergic sensitization in infants with atopic eczema from different countries. Allergy. 2009;64:295-303.
75. Alduraywish SA, Lodge CJ, Vicendese D, Lowe AJ, , Erbas B, Matheson MC, Hopper J, Hill DJ, Axelrad 3, Abramson MJ, Allen KJ, , Dharmage SC. Sensitization to milk, egg and peanut from birth to 18 years: A longitudinal study of a cohort at risk of allergic disease. Pediatr Allergy Immunol. 2016 Feb;27(1):83-91.
76. Yavuz ST, Sahiner UM, Buyuktiryaki B, Soyer OU, Tuncer A, Sekerel BE, Kalayci O, Sackesen C. Phenotypes of IgE-mediated food allergy in Turkish children. Allergy Asthma Proc. 2011 Nov-Dec;32(6):47-55.
77. Eigenmann PA, Calza AM. Diagnosis of IgE-mediated food allergy among Swiss children with atopic dermatitis. Pediatr Allergy Immunol. 2000 May;11(2):95-100.
78. Twaroch TE, Curin M, Valenta R, Swoboda I. Mold allergens in respiratory allergy: from structure to therapy. Allergy Asthma Immunol Res. 2015 May;7(3):205-20.
79. Fukutomi Y, Taniguchi M. Sensitization to fungal allergens: Resolved and unresolved issues. Allergol Int. 2015 Oct;64(4):321-31.
80. Crameri R, Zeller S, Glaser AG, Vilhelmsson M, Rhyner C. Cross-reactivity among fungal allergens: a clinically relevant phenomenon? Mycoses. 2009 Mar;52(2):99-106.
81. Sönmez Tamer G1, Çalışkan S. [Prevalence of house dust mite allergy in cases with atopic disease symptoms in Kocaeli province, Turkey]. Mikrobiyol Bul. 2009 Apr;43(2):309-12.
82. Hasnain SM, Al-Frayh AR, Subiza JL, Fernández-Caldas E, Casanovas M, Geith T, Gad-El-Rab MO, Koshak E, Al-Mehdar H, Al-Sowaidi S, Al-Matar H, Khouqeer R, Al-Abbad K, Al-Yamani M, Alaqi E, Musa OA, Al-Sedairy S. Sensitization to indigenous pollen and molds and other outdoor and indoor allergens in allergic patients from Saudi Arabia, United Arab Emirates, and Sudan. World Allergy Organ J. 2012 Jun;5(6):59-65.

83. Akhapkina IG, Krakhanenkova SN, Mamlenkova EA, Dobronravova EV, Shushpanova EN. [Incidence of hypersensitivity to mycotic and mite allergens]. *Klin Lab Diagn*. 2009 Jul;(7):33-5.
84. Peat JK, Tovey E, Toelle BG, Haby MM, Gray EJ, Mahmic A, et al. House dust mite allergens. A major risk factor for childhood asthma in Australia. *Am J Respir Crit Care Med* 1996; 153(1):141-6.
85. Ariano R, Canonica GW, Passalacqua G. Possible role of climate changes in variations in pollen seasons and allergic sensitizations during 27 years. *Ann Allergy Asthma Immunol*. 2010 Mar;104(3):215-22.
86. D'Amato G, Bergmann KC, Cecchi L, Annesi-Maesano I, Sanduzzi A, Liccardi G, Vitale C, Stanziola A, D'Amato M. Climate change and air pollution: Effects on pollen allergy and other allergic respiratory diseases. *Allergo J Int*. 2014;23(1):17-23.
87. Miri A, Ahmadi H, Ghanbari A, Moghaddamnia A: Dust Storms Impacts on Air Pollution and Public Health under Hot and Dry Climate. *IJEE* 2007, 1:101–105.
88. Nabavizadeh SH, Anushiravani A, Amin R. Natural rubber latex hypersensitivity with skin prick test in operating room personnel. *Iran J Allergy Asthma Immunol*. 2009 Dec;8(4):219-20.
89. Miri S, Pourpak Z, Zarinara A, Heidarzade M, Kazemnejad A, Kardar G, Firooz A, Moin A. Prevalence of type I allergy to natural rubber latex and type IV allergy to latex and rubber additives in operating room staff with glove-related symptoms. *Allergy Asthma Proc*. 2007 Sep-Oct;28(5):557-63.
90. Ghasemi IM, Rezaee M, Jonaidi Jafari N, Izadi M. Latex gloves allergy in dental workers, Iran. *Pak J Biol Sci*. 2007 Apr 1;10(7):1068-72.
91. Moghtaderi M, Farjadian S, Momeni Z, Najib K. Natural latex sensitization and respiratory function among workers in latex glove factories: a pilot study. *J Occup Environ Hyg*. 2012;9(10):D183-5.
92. Bemanian MH, Farhoudi A, Pourpak Z, Gharagozlou M, Movahedi M, Nabavi M, Mozafari H, Mohammadzadeh I, Chavoshzadeh Z, Shirkhoda Z. Systemic and local reactions of bee venom immunotherapy in Iran. *Iran J Allergy Asthma Immunol*. 2007 Dec;6(4):203-6.

Figure Legend:

Figure 1. Location of most populated cities in map of Iran

Figure 2: Flow diagram our studies in systematic review and meta-analysis

Figure 3: Forest plot of prevalence of animal allergens among Iranian patients with allergy

Figure 4: Forest plot of meta-analysis results for prevalence of food allergens

Figure 5: Forest plot of prevalence of fungi allergens among Iranian patients with allergy

Figure 6: Forest plot of prevalence of house dust mites (HDM) allergens among Iranian patients with allergy

Figure 7: Forest plot of prevalence of pollen allergy among Iranian patients with allergy

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Table 1: Characteristics of studies included in the meta-analysis for prevalence of sensitization to common allergens in Iran

Study, Year (reference)	City	N (patients)	Age (mean)	Male (%)	Animal (%)	Cockroach (%)	Food (%)	Fungi (%)	HDM (%)	Pollen (%)
Abdollahi-Fakhim et al. , 2014(21)	Tabriz	106	6.5	50	12	NR	26	10	23	35
Ahanchian et al. ,2016(22)	Mashhad	371	5.3	54	NR	NR	100	NR	NR	NR
Ahmadiafshar et al. ,2008 (23)	Zanjan	200	28.2	44	12	15	9	12	16	41
Akbari et al. , 2000 (24)	Isfahan	1077	NR	NR	NR	20	NR	37	35	48
Amirmajdi et al. ,2011(25)	Mashhad	58	29.8	45	NR	NR	NR	53	NR	NR
Arshi et al. ,2009 (26)	Tehran	245	26.4	48	NR	NR	NR	50	64	92
Assarehzadegan et al. ,2013(27)	Ahvaz	299	32	52	NR	30	NR	24	43	89
Behmanesh et al. ,2010(28)	Mashhad	133	7.8	62	9	6	NR	NR	19	57
Bemanian et al. ,2012(29)	Yazd	95	22.7	55	NR	13	NR	NR	8	NR
Bonyadi et al.,2014(30)	Tabriz	90	29	44	NR	NR	NR	24	NR	NR
Farajzadeh et al. ,2010 (31)	Kerman	51	<5	63	NR	NR	62	NR	NR	NR
Farhoudi et al. ,2002(32)	Tehran	100	6.2	68	2	29	10	NR	31	33
Farhoudi et al. ,2005(33)	Tehran	226	13.5	55	NR	25	NR	NR	19	62
Farjadian et al.,2012(34)	Shiraz	79	3	56	NR	NR	15	NR	NR	NR
Farrokhi et al. ,2015(35)	Bushehr	743	27.2	53	78	NR	NR	82	88	77
Fazlollahi et al.,2007 (36)	Tehran	250	11.7	52	NR	NR	14	NR	NR	NR
Fereidouni et al. ,2009 (37)	Mashhad	306	25.6	47	NR	21	NR	8	20	77
Fouladseresht et al. ,2014 (38)	Kerman	157	NR	49	7	12	21	6	8	22
Ghafari et al.,2010 (39)	Sari	375	13.5	34	7	15	NR	3	25	4
Hosseini et al. ,2014(40)	Tehran	313	5.7	62	15	18	21	26	22	26
Kashef et al. ,2003 (41)	Shiraz	212	18.2	50	NR	NR	NR	8	22	92
Khazei et al. ,2003 (42)	Zahedan	1285	2 to 79	43	70	NR	30	65	89	43
Khazei et al. ,2015(43)	Zahedan	478	15 to 70	58	26	25	NR	53	51	30
Khosravi et al. ,2009 (44)	Tehran	180	NR	NR	NR	NR	NR	54	NR	NR
Mahram et al. ,2013 (45)	Qazvin	163	24.6	42	25	NR	NR	26	20	58
Moghtaderi et al. ,2009 (46)	Shiraz	230	6.3	76	NR	NR	NR	10	NR	NR
Moghtaderi et al.,2012 (47)	Shiraz	90	1.6	53	NR	NR	40	NR	NR	NR
Moghtaderi et al.,2015 (48)	Shiraz	50	32	20	NR	NR	58	NR	NR	NR
Moghtaderi et al.,2015 (49)	Shiraz	656	27.6	44	16	30	NR	16	34	64
Moghtaderi et al. ,2016 (50)	Shiraz	200	21.1	35	36	NR	NR	NR	NR	NR
Mohammadi et al.,2008 (51)	Tehran	206	18	52	NR	NR	5	NR	NR	NR
Mohammadzadeh et al. ,2012 (52)	Babol	180	6.8	52	NR	NR	NR	NR	61	NR
Movahedi et al. ,2000 (53)	Tehran	400	19	52	NR	NR	NR	NR	NR	57
Nabavi et al. ,2009 (54)	Semnan	298	10	NR	NR	NR	30	NR	NR	NR
Nabavi et al. ,2010 (55)	Semnan	220	<18	60	NR	NR	NR	35	NR	NR
Nabavizadeh et al. ,2013 (56)	Yasuj	184	23.7	65	23	35	33	48	8	37

Onsori et al. 2016(57)	Tehran	282	25	40	NR	NR	31	NR	NR	NR
Pourpak et al. 2003 (58)	Tehran	190	4.8	58	NR	NR	53	NR	NR	NR
pourpak et al. 2004 (59)	Tehran	119	0.1 to 12	NR	NR	NR	44	NR	NR	NR
Safari et al. 2009 (60)	Shiraz	92	2.7	64	18	25	19	10	27	27
Salehi et al. 2009 (61)	Tehran	100	2.7	71	NR	NR	39	NR	NR	NR
Shakurnia et al. 2012(62)	Ahvaz	407	31.5	52	NR	32	NR	NR	23	NR
Shakurnia et al. 2014 (63)	Ahvaz	111	30.7	51	NR	38	NR	32	41	86
Varasteh et al. 2007(64)	Mashhad	38	38	NR	NR	NR	70	NR	NR	NR

HDM=House Dust Mites, NR=Not Reported

Table 2. Frequency of allergens differentiated by type of allergen and major cities of Iran

Allergen types	Cites	Tehran	Mashhad + Semnan	Tabriz + Zanjan + Qazvin	Shiraz	Ahvaz	Coastal areas	Kerman + Yazd + Isfahan	All Cities
Cockroach	Prevalence	23.9	13.7	25.3	32.2	32.0	15.7	16.0	25.1
	95% CI	19.2-28.6	3.7-28.8	4.8-45.8	24.4-40.0	28.6-35.5	7.7-23.7	10.6-21.4	20.1-30.2
Food	Prevalence	4.9	5.1	3.1	4.2	NES	4.0	3.6	14.6
	95% CI	2.6-7.2	3.2-7.0	9.0-7.2	4.0-68.0		3.2-4.8	0.8-7.9	12.2-17.0
Fungi	Prevalence	40.0	3.2	9.4	10.3	13.1	33.5	NES	19.6
	95% CI	13.5-66.4	16.4-52.2	6-18.2	1.8-18.7	3.0-23.3	26-39.8		14.2-25.0
Pollen	Prevalence	44.5	55.0	32.5	48.1	83.1	35.1	25.1	44.8
	95% CI	23.6-65.3	7.8-65.4	28.0-37.0	22.2-74.1	79-86.7	4.8-65.4	7.2-52.0	37.1-52.5
Animal	Prevalence	13.7	9.0	14.5	15.5	NES	48.1	5.4	19.5
	95% CI	8.9-18.8	4.1-13.9	10.7-18.4	13.2-17.9		18.0-78.2	1.9-8.9	9.1-29.9
House dust mites	Prevalence	34.1	17.5	16.1	25.3	40.8	63.2	16.7	33.4
	95% CI	13.4-54.8	13.9-21.0	9.8-22.4	10.8-39.8	26.3-55.3	40.3-86.1	7.3-37.1	24.0-43.0

NES=Not Enough Studies, Coastal areas= (Babol, Busher, Sari, Zahedan)

Table3. Prevalence of allergens according to allergens type and age group

Allergens	Number of study	Prevalence% (95% CI)			Q-test		
		<5 yr	5-16 yr	>16 yr	value	I-square	P
Animal	14	NES	8.4 (4.6-12.2)	35.8 (15.0-56.7)	3.01	99.6%	0.002
Cockroach	16	NES	7.1 (6.1-8.0)	3.2 (2.5-3.9)	40.75	94.4%	<0.001
Food	21	26.2 (22.8-29.7)	11.3 (9.8-12.9)	2.8 (2.1-3.5)	265.8	95.8%	<0.001
Fungi	15	NES	4.2 (3.3-5.1)	5.3 (4.6-6.0)	3.31	78.3%	0.069
HDM	23	NES	5.2 (4.4-6.0)	8.1 (7.4-8.8)	4.3	93.2%	<0.001
Pollen	21	NES	3.7 (3.0-4.4)	8.4 (7.7-9.1)	85.7	98.3	<0.001

NES=Not Enough Study, CI=Confidence Interval, yr=year

Table 4: The results of Egger's test to assess publication bias in subgroup allergens

Allergens	Numer of studies	bias	p
Animal allergens	13	-18.80	0.37
Cockroach	15	2.79	0.24
Food allergens	17	3.87	0.053
Fungi	21	-2.72	0.70
House dust mites	16	-10.3	0.09
Pollen	20	-6.31	0.40
Overall	-	2.96	0.06

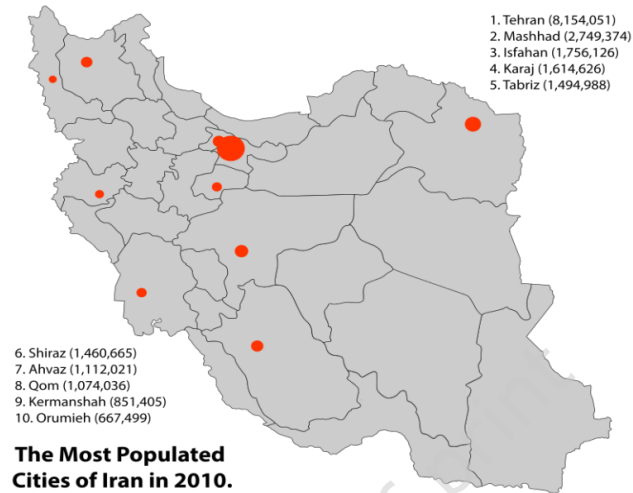


Figure 1. Location of most populated cities in map of Iran

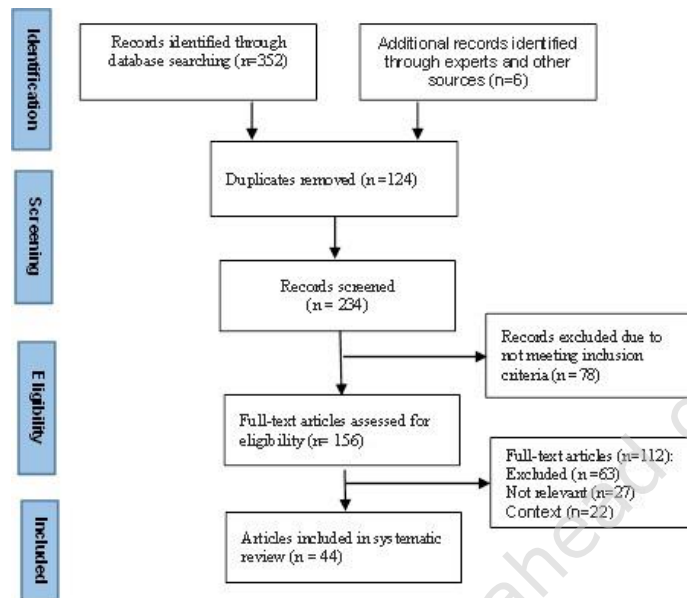


Figure 2: Flow diagram of the identification of literature for selection of studies in systematic review and meta-analysis

