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Article type : Review

Outdoor pollen is a trigger of child and adolescent asthma ED presentations: a systematic review and meta-analysis

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Running title: Review of pollen on asthma ED visits in children and teens

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ABSTRACT

Background: In the context of increased asthma exacerbations associated with climatic changes such as thunderstorm asthma, interest in establishing the link between pollen exposure and asthma hospital admissions has intensified. Here, we systematically reviewed and performed a meta-analysis of studies on pollen and ED attendance.

Methods: A search for studies with appropriate search strategy in Medline, Embase, Web of Science and CINAHL was conducted. Each study was assessed for quality and risk of bias. The available evidence was summarised both qualitatively and meta-analysed using random effects models when moderate heterogeneity was observed.

Results: Fourteen studies were included. The pollen taxa investigated differed between studies, allowing meta-analysis only of the effect of grass pollen. A statistically significant increase in the percentage change in the mean number of asthma ED presentations (MPC) (pooled results from three studies) was observed for an increase in 10 grass pollen grains per cubic meter of exposure 1.88% (95%CI = 0.94%, 2.82%). Time series studies showed positive correlations between pollen concentrations and ED presentations. Age stratified studies found strongest associations in children aged 5 to 17 years old.

Conclusion: Exposure to ambient grass pollen is an important trigger for childhood asthma exacerbations requiring ED attendance. As pollen exposure is increasingly a problem especially in relation to thunderstorm asthma, studies with uniform measures of pollen and similar analytical methods are necessary to fully understand its impact on human health.

Key words: Asthma, Pollen, Aeroallergens, Acute Exacerbations, Emergency medical services

Abbreviations: ED: emergency department; WAO: World Allergy Organization;

Author Contributions: BE, MA, SD developed the research question and review protocol. MJ, KL, RT conducted search and initial review for article inclusion. MJ, BE, KL qualitatively synthesized the included studies. KL, LP was responsible for meta-analysis and KL, LP and BE interpreted analysis. KL, MJP conducted the quality assessment. JD, EN, CK contributed to interpreting the qualitative synthesis and meta-analysis. BE, MJ, KL, SD drafted the manuscript. BE, MJ, KL, RT, JD, EN, MA, SD were involved in the revisions of the manuscript. All authors read and approved the final manuscript before submission. BE and SD accept full responsibility for this work and act as guarantors for the study.

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INTRODUCTION

Asthma is one of the most prevalent diseases in industrialised societies, particularly among children and adolescents (1). Reports from the World Allergy Organization (2) indicate a steady increase of asthma prevalence globally especially in "Westernised" countries such as Australia, UK and the US, where a high proportion of this increase occurs in children and young adults. The global burden of asthma is estimated to affect 300 million people (1) and prevalence is higher in 0 to 14 year old males (11.4%), but is higher among females aged 15 years or older (3).

Medications usually control persistent asthma; however up to 30% of children who experience severe exacerbations require emergency department (ED) care (3). Exacerbations can be triggered by respiratory viral infections, air pollutants, exercise, tobacco smoke, non-compliance with preventive medications, exposure to irritant chemicals and/or aeroallergens such as fungal spores and pollen (4-6). Understanding the major triggers of asthma exacerbations among children and adolescents that result in ED presentations could potentially lead to improved prevention strategies.

There is a gap in our understanding of changing outdoor environment and respiratory disease, especially in cities with dangerous environmental conditions such as the "Thunderstorm Asthma" outbreak that occurred in Melbourne, Australia, that was fatal (7). In some cities, pollen seasons are severe with temperamental weather patterns and large volumes of pollen being dispersed in the air. For example, in Melbourne Australia grass pollen levels peaked at 207 grains/m^3 and were well above 50 grains/m^3 (defined as high pollen days) for a significant proportion of the grass pollen season during October 2009 and December 2011 (5). Recent climate changes, characterised by frequent changes in weather patterns and extended periods of extreme rainfall and heat, are predicted to be impacting on intensity and duration of the pollen season.

High pollen days during peak pollen seasons combined with changing climatic conditions can cause serious attacks requiring emergency department presentations or subsequent hospital admission. Increasingly studies are examining associations between ambient pollen concentrations and risk of asthma exacerbations (5, 8-12). Therefore, synthesizing the current literature to better understand the role of different types of pollen exposure on asthma exacerbations is important for health and promoting interventions to reduce the burden directly associated with ambient pollen. No systematic synthesis of such evidence has been conducted to date. The aim of this systematic review was to synthesize the current evidence of pollen as a trigger for child and adolescent asthma ED attendances and perform meta-analysis where possible.

METHODS

This systematic review was undertaken following both the PRISMA (13) and MOOSE (14) guidelines for reporting systematic review and meta-analysis.

Search strategy

The focus of the search was to identify articles that examined the effects of outdoor pollen exposure on asthma exacerbations in children and adolescents requiring ED attendance. The peer-reviewed literature was searched using the Medline, Embase, Web of Science and CINAHL (EBSCO) databases, 1966 to 2017. Medical Subject Headings (MeSH) search terms used were related to exposure (pollen); outcome (emergency*, asthma*) and population (child*, pediatric* or paediatric*) combined. Further hand searches were conducted using citations from the identified and related review papers. After reviewing the abstract of the identified journal articles, if all inclusion criteria were met, the full text were read for inclusion or exclusion.

Eligibility criteria

Inclusion criteria were human subjects and published in English. Study populations were children and adolescents aged less than 18 years who attended an ED with a diagnosis of asthma. Studies must have reported exposure to outdoor levels of pollen.

Data extraction and assessment

From each study included, data regarding study design, method of analysis, study location, time period of the study, method of pollen collection, age range and number of children, exposure definition (pollen species such as grasses, weeds, trees and conifers), pollen count, outcome definition, effect estimates together with 95% confidence intervals were extracted where available. A quality assessment of each study was conducted independently by two researchers using a quality assessment framework developed by Zaza et al (15). Quality assessment examined selection and description of the study sample, outcome assessment, exposure assessment, appropriateness of statistical methods and adjustment for confounders.

Assessment for Meta-analysis

Of the articles included in the review, we only considered studies with grass pollen as the primary exposure for inclusion in the meta-analysis because of the limited number of estimates for the other pollen types. To enable greater comparison, effect estimates were standardised to an increase per 10 grains/m^3 of grass pollen and the transformed variances computed using the delta method (16). Meta-analyses of the chosen studies were carried using linear mixed effects models that assumed the presence of a random effect where the DerSimonian-Laird estimator was used to estimate the variance parameter (17). Stratification analyses were not possible due to the limited number of studies. The analyses were undertaken using the R package metafor (18) and statistical software STATA version 14.1 (Stata Corp LP, College Station, TX, USA) was used to create forest plots of these analyses.

Exposure assessment - Pollen monitoring methods

Daily pollen counts are given as grains/m^3 over a 24 hour period. Where reported, the two instruments used for pollen counts were Rotorod Samplers (Sampling Technologies, MN, USA) and Burkard Volumetric traps (Burkard, Hertfordshire, UK). There are differences in the efficiency of these instruments for pollen collection (19).

RESULTS

Search Results

Electronic and hand searching yielded 227 articles after duplicates were removed, of which 213 were excluded (Figure 1). We identified 14 eligible studies where pollen was considered the primary exposure variable.

Characteristics of the Studies

In Table 1 we describe the study design, location of the study, time period, method of pollen collection/measurement, sample size of the study, and the age group of the participants if reported. Studies were from a number of different regions in the world, predominately in the

USA and Canada (8, 9, 10, 11, 20-24), Spain (12, 25) and Australia (5, 26). One earlier study was conducted in Tel Aviv in Israel (27).

Pollen exposure in these studies was classified into four broad groups; grass, tree, weed, and conifer following the guidelines of Weber (28). Of these 14 studies: two reported grass pollen exposure only (5, 26); one reported tree pollen exposure only (20); one reported tree and weed pollen exposures (10); seven reported grass, tree and weed pollen exposures (9, 11, 21-25); and three studies reported pollen from all these categories (8, 12, 27).

Quality Assessment

The included studies appeared to have an overall moderate risk of bias. The main sources of bias arises from the inclusion of children aged <2 years, with whom diagnosis of asthma is very difficult and prone to misclassification. Only one study (21) did not include children aged <2 years, while three studies (8, 20, 24) reported age stratified results. The method of pollen sampling varied between studies with six using the Burkard volumetric pollen and spore trap (5, 10, 12, 20, 22, 25), four using the Rotorod smapler (8, 9, 11, 27) and three not stating the instrument used (21, 23, 24). One study did not use pollen counts, instead compared emergency department visits in the pollen season to those not in the pollen season (26). The ambient pollen concentration for each day was assumed to be every individuals' exposure due to lack of individual level pollen data. All but two studies (12, 25) used data from a single collection site. Reporting bias is evident in some studies that investigated multiple lag points but reported only on the most significant associations (11, 12). Potential confounding bias from the lack of adjustment for individual level variables such as sensitization to pollen or other allergens also contributed to low levels of the quality of the studies included.

Synthesis of findings

A summary of the findings from each study is presented in Table 2. Two studies (5, 25) utilized non-linear modelling to investigate short-term effects of different types of pollen on child asthma ED visits. Erbas et al (5) found a threshold level of 20 grains/m^3 for grass pollen in child asthma ED presentations in Melbourne. To add to the findings from Erbas et al (5), Tobias et al (25) reported the threshold level for weed pollen was 37 grains/m^3 and for tree pollen was 13 grains/m^3.

Lierl & Hornung (11) examined exposure to grass, trees and weeds among children and adolescents attending emergency department in Cincinnati, USA using a Poisson regression of incidence on a given day of exposure. Although they reported total pollen effects of log pollen lagged 3 days RR=1.089 (95% CI 1.027-1.155) they did not present results for different pollen types.

Some studies used mean percentage change (MPC) to report the estimated effects. In examining the effects of daily levels of grass pollen on ED presentations, Tobias et al (12) found significant associations for 3-day lag period exposure to grasses which resulted in a 17.1%. MPC increase in ED presentations (95%CI: 3.2-32.8) for an increase of ~100 grains/m^3 of grass pollen (this figure was obtained as the 95-99th percentile increase in the pollen level in Madrid). In Montreal, Canada, Heguy et al (9) also identified a significant increase of 1.73 % MPC in ED presentations (95%CI: 0.24-3.25) at 3-day lag of an increase of 10 grains/m^3. They stratified their analysis by first visit to ED or readmission to ED and found the relationship between grass pollen levels and ED visits was stronger during the first visit (lag 3: 2.08 95%CI: 0.28-3.91; lag 5: 1.43 95%CI: 0.09-3.76). Babin et al (24) also found an increase in paediatric (1-17 years old) ED visits at 3-lag with an increase of 10 grains/m^3 of grass pollen (MPC: 2.6; 95%CI: 0.3-5.0). They further stratified results into three age groups, 1-4, 5-12, 13-17, presenting only the results for those aged 5-12 years old. The effect of pollen on ED visits was consistently stronger in this age group. An increase in 100 grains/m^3 of tree pollen showed an increase of 1.8% MPC (95%CI 0.9-2.6) in ED visits on the day (lag 0). This association attenuated, though remaining significant, as the lag increased. Conversely, the relationship between grass pollen counts and ED visits strengthened with increasing lag, up to 3 days after which it abruptly drops off (lag 0: 1.6 95%CI: -2, 5.4; lag 1: 3.5 95%CI: 0.1, 7.1; lag 2: 4.3 95%CI: 0.9, 7.9; lag 3: 5.5 95%CI: 2.2, 9; lag 4: 3.1 95%CI: -0.5, 6.8).

Amongst the four descriptive time-series studies (10, 22, 26, 27) investigating the associations between airborne pollen levels and ED presentations, Jariwala and colleagues (10) found that when tree pollen was the major airborne pollen type in the area, the highest daily number of ED visits for children was observed. Averaging pollen counts and ED visits over a seven year period, Jariwala et al (22) found tree pollen counts to be significantly correlated with paediatric asthma related ED visits during the peak pollen season (rho=0.28, p<0.001). This association persisted throughout the year (excluding the winter months) (rho=0.33, p<0.001). In inland Australia, Hayden and Muscatello (26) reported that peak asthma count days for children (defined as top 0.1 percentile for daily asthma ED presentations over 13 years at nine inland New South Wales hospitals) corresponded with the rye grass season. No formal statistical tests were used to assess the differences overall or by specific age group. A two-year study conducted in Wilmington, Delaware in the USA categorized the rate of paediatric ED presentations into low and high levels defined as the percent of the overall average monthly value (23). They looked at effects of air pollutants, pollen and meteorological factors with multiple comparisons and t-tests. They found tree and weed pollen counts were higher on days with ≥ seven asthma-related ED visits (p=0.05), but no significant difference in grass pollen counts between high- and low-visit days.

In their single taxon models investigating linear effects of pollen on ED presentations in Atlanta, USA, Darrow and colleagues (8) found a positive association between a variety of pollen types and risk of ED presentations. In age specific investigations, they found that children aged 5-17 years showed the strongest association with oak (Quercus species) pollen (RR=1.046; 95%CI: 1.033 to 1.059 per standard deviation (SD) increase in pollen concentration). This result is supported by a recent study (20), that also showed a positive association between ED visits and oak pollen that was strongest amongst children aged 5 – 17 years. Ito et al. (20) also examined a number of other single taxon models, which showed, in general, highly positive associations in the 5-17 years age group with ash pollen (RR= 2.6 95%CI: 2.1 to 3.1 per 0-to-98th percentile increase for ash pollen). Gleason et al (21) showed grass pollen to only be minimally associated with paediatric asthma ED visits, while tree and weed pollen were strongly associated.

Meta-analysis

Although many studies reported estimated effects, conducting meta-analysis was difficult for studies reporting relative risk and odds ratios because no two studies reporting these estimates used the same pollen type or same lag day average. However, we could conduct a meta-analysis for studies reporting mean percentage change in ED presentations (9, 12, 24). All studies reported on a three day lag, two reported the estimated effect per increase in 10 grains/m^3 of pollen (9, 24) and we were able to transform estimated effect for the other study (12) and perform a meta-analysis (Figure 2). Meta-analysis showed a significant increase in MPC of ED presentations (MPC=1.88 95%CI:0.94-2.82, p = 0.001) associated with an increase of 10 grains/m^3 of grass pollen. The measure of heterogeneity was very close to zero.

DISCUSSION

In this systematic review of a variety of pollens and meta-analysis of grass pollen, we have presented evidence of effects of pollen, especially of grass, on child asthma ED presentations from various regions around the world. An increase in risk of childhood asthma ED presentations between 1% and 14% was observed when pollen was the primary exposure. Higher concentrations of grass pollen were associated with daily increases in ED visits for asthma up to 3 days after exposure. In some places, the minimum threshold of grass pollen exposure, at which sensitised individuals may experience symptoms was as low as 10 grains/m^3 per day. The observed pooled effect of 1.88% per 10 grains/m^3 suggested that increased levels of grass pollen 3-days prior was associated with increased ED presentations for childhood asthma (MPC 1.88% [0.94, 2.82] per 10 grains/m^3). If pollen levels at lag 3 were 20 grains/m^3 higher than baseline, then we would expect a 3.76% increase in ED presentations for childhood asthma. If pollen levels three days prior (lag 3) were 50 grains/m^3 higher than baseline, then we would expect a 9.4% increase in ED presentations for childhood asthma. A wide range of pollen levels during the pollen seasons can occur such as the maximum level of 106.5 grains/m^3 as reported by one of the studies included in the meta-analysis. This gives a 18.8% increase in MPC, which would be a clinically important change in the expected ED presentations for hospital planning purposes. However, typically the estimated risk was highly dependent on the methodological approach undertaken to assess these associations. The non-linear effects of pollen reported in two studies (5, 25) indicated a positive association between the grass pollen and asthma ED presentations up to a threshold, after which the effect flattened off. However, the threshold level is somewhere between 20 and 50 grains/m^3.

The possibility that local variations in pollen levels, pollen types and pollen combinations across areas affecting child and adolescent asthma ED presentations should also be considered in such studies. In Australia, grass pollen seems to be an important trigger (5), trees and weeds in various regions in the USA (20, 23), grass and weeds in Canada (9) and grass and olive tree pollen in Madrid, Spain (12, 25). The location of pollen count stations will also contribute to variations in the levels and types of pollen measured (29No study reported on the percentage of children/adolescents who were first diagnosed with asthma

following the ED visit after high pollen load exposure; whether the children had a prior diagnosis of allergic rhinitis; or were undergoing allergen specific immunotherapy.
While some of study areas now have pollen monitoring and prediction programs either app based or website (such as Melbourne, Australia); these are only recently available to the public and did not exist when many of the studies were conducted. It is only the most recent studies that could have been impacted by these programs.

There are a number of limitations associated with combining studies investigating the effects of pollen on child and adolescent asthma ED presentations. There was inter-study variation in the types of pollens examined at the taxa level, such as grasses, trees, conifers and weeds; also at the species level, such as different species of grasses, trees, conifers or weeds. To further complicate this, there was likely to have been geographic and seasonal variation in species of vegetation that produced pollens. Analysis of pollen at a high taxa level (e.g. 'grasses', 'weeds' or 'trees') may have included different species in different sites making comparability difficult to ascertain. Different statistical analytical methods made it difficult to compare the results of studies which used nonlinear models with no estimated effects with correlational studies. In addition, there were differences in the cut-off points for age groups between studies. This raised potential diagnosis misclassification bias associated with possible misdiagnosis of asthma in the 0-2 years age group due to the ambiguity of the respiratory symptoms in this age group (30). Some studies combined the age groups; which made it difficult to untangle any age specific effects that may modify the associations.

Variations in ecological and climatic conditions may also contribute to the differences observed. All studies reporting significant effect sizes were from highly urbanized regions. In some regions with high levels of urbanisation, greater traffic flow and increased levels of traffic related air pollutants may provide greater risk even during low pollen periods. Conversely, during peak pollen periods these environmental factors may interact thereby further increasing the likelihood of an ED presentation for asthma. Pollen is also dependent on changing climatic conditions and its effect will vary by climatic region (31).

There are different methods for measuring pollen such as the Rotorod sampler and Burkard pollen and spore trap. These two methods of pollen sampling have different efficiency for different particle sizes (19). According to Frenz (19), both Rotorod and Burkard volumetric samplers are affected by wind speed. The maximum change in collection efficiency could be up to 40%. These two instruments are affected by wind speed in fundamentally different ways and this can lead to potential measurement and ascertainment bias. All these variations make it difficult to compare the studies with each other directly.

Our upper airways carry air into our lungs and consecutive days of high pollen trigger swelling of these airways constricting our breathing. Among asthmatics, this can be fatal as there is further restriction of air getting into the lungs. High pollen days during peak pollen seasons combined with changing climatic conditions can cause serious and widespread asthma attacks requiring emergency department presentations or subsequent hospital admission. In the situation of Thunderstorm Asthma" many individuals experience severe symptoms due to grass pollen exposure, up to 60% of whom were previously known to suffer from allergic rhinitis without prior diagnosis of asthma (7).

Our qualitative synthesis and meta-analysis show increasing evidence that children and adolescents exposed to outdoor pollen may be at an increased risk of asthma exacerbations requiring emergency department presentation. Given this risk, simple yet effective interventions for the management of asthma exacerbations could be developed. This an important and timely review because many simple and cost effective local public health preventative strategies can avoid pollen exposures during pollen seasons such as planting non-allergenic plants, not mowing grass and staying indoors on high pollen days. In some cities, including Melbourne, media alerts of high pollen day forecasts are implemented in mass media campaigns and public health networks during the pollen seasons. At the primary care level, better understanding risk will enable health professionals to direct patients to be diligent with medication use as a precautionary measure. For some, clinical interventions such as immunotherapy may be necessary.

In summary, pollen of different taxa is an important risk factor for asthma exacerbations and one of the few modifiable environmental exposures. Guided by clinicians and inter-agency pollen monitoring alert systems, early warnings of high-danger periods could be developed and avoidance measures incorporated by families for "at risk" children.

REFERENCES

1. Asher I, Pearce N. Global burden of asthma among children. *Int J Tuberc Lung Dis* 2014;**18**(11):1269-1278.

2. Pawankar R, Canonica GW, Holgate ST, Lockey RF, Blaiss MS. World Allergy Organization (WAO) White Book on Allergy: Update 2013. Milwaukee, Wisconsin, USA: World Allergy Organization; 2013.

3. Australian Centre for Asthma Monitoring. Asthma in Australia 2011. AIHW Asthma Series no. 4. Cat. no. ACM 22. Canberra: AIHW; 2011.

4. Eggleston PA. Complex interactions of pollutant and allergen exposures and their impact on people with asthma. *Pediatrics* 2009;**123 Suppl 3**:S160.

5. Erbas B, Akram M, Dharmage S, Tham R, Dennekamp M, Newbigin E, et al. The role of seasonal grass pollen on childhood asthma emergency department presentations. *J Allergy Clin Immunol* 2012;**42**(5):799-805.

6. Strickland MJ, Darrow LA, Klein M, Flanders WD, Sarnat JA, Waller LA, et al. Short-term associations between ambient air pollutants and pediatric asthma emergency department visits. *Am J Respir Crit Care Med* 2010;**182**(3):307.

7. State of Victoria. Review of response to the thunderstorm asthma event of 21–22 November 2016. Final Report. Inspector-General for Emergency Management. Melbourne, Victoria: 2017. Available from: https://www2.health.vic.gov.au/emergencies/thunderstorm-asthma-event/review

8. Darrow LA, Hess J, Rogers CA, Tolbert PE, Klein M, Sarnat SE. Ambient pollen concentrations and emergency department visits for asthma and wheeze. *J Allergy Clin Immunol* 2012;**130**(3):630-638.e634.

9. Heguy L, Garneau M, Goldberg MS, Raphoz M, Guay F, Valois MF. Associations between grass and weed pollen and emergency department visits for asthma among children in Montreal. *Environ Res* 2008;**106**(2):203-211.

10. Jariwala SP, Kurada S, Moday H, Thanjan A, Bastone L, Khananashvili M, et al. Association between tree pollen counts and asthma ED visits in a high-density urban center. *J Asthma* 2011;**48**(5):442-448.

11. Lierl MB, Hornung RW. Relationship of outdoor air quality to pediatric asthma exacerbations. *Ann Allergy Asthma Immunol* 2003;**90**(1):28-33.

12. Tobias A, Galan I, Banegas JR, Aranguez E. Short term effects of airborne pollen concentrations on asthma epidemic. *Thorax* 2003;**58**(8):708-710.

13. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Int J Surg* 2010;**8**(5):336-341.

14. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;**283**(15):2008.

15. Zaza S, Wright-De Agüero LK, Briss PA, Truman BI, Hopkins DP, Hennessy MH, et al. Data collection instrument and procedure for systematic reviews in the guide to community preventive services. *Am J Prev Med* 2000;**18**(1, Supplement 1):44-74.

16. Casella G, Berger RL. Statistical Inference: Brooks/Cole Publishing Company; 1990.

17. Dersimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**(3):177-188.

18. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. *Journal of Statistical Software* 2010;**36**(3):48.

19. Frenz DA. Comparing pollen and spore counts collected with the Rotorod Sampler and Burkard spore trap. *Ann Allergy Asthma Immunol* 1999;**83**(5):341-347.

20. Ito K, Weinberger KR, Robinson GS, Sheffield PE, Lall R, Mathes R, et al. The associations between daily spring pollen counts, over-the-counter allergy medication sales, and asthma syndrome emergency department visits in New York City, 2002-2012. *Environ Health* 2015;**14**:71.

21. Gleason JA, Bielory L, Fagliano JA. Associations between ozone, PM2.5, and four pollen types on emergency department pediatric asthma events during the warm season in New Jersey: a case-crossover study. *Environ Res* 2014;**132**:421-429.

22. Jariwala S, Toh J, Shum M, De Vos G, Zou K, Sindher S, et al. The association between asthma-related emergency department visits and pollen and mold spore concentrations in the Bronx, 2001-2008. *J Asthma* 2014;**51**(1):79-83.

23. Wang HC, Yousef E. Air quality and pediatric asthma-related emergencies. *J Asthma* 2007;**44**(10):839-841.

24. Tobias A, Galan I, Banegas JR. Non-linear short-term effects of airborne pollen levels with allergenic capacity on asthma emergency room admissions in Madrid, Spain. *Clin Exp Allergy* 2004;**34**(6):871-878.

25. Babin S, Burkom H, Holtry R, Tabernero N, Davies-Cole J, Stokes L, et al. Medicaid patient asthma-related acute care visits and their associations with ozone and particulates in Washington, DC, from 1994-2005. *Int J Environ Res Publ Health* 2008;**18**(3):209-221.

26. Hayden TJ, Muscatello DJ. Increased presentations to emergency departments for asthma associated with rye grass pollen season in inland NSW. *NSW Public Health Bulletin* 2011;**22**(8):154-158.

27. Garty BZ, Kosman E, Ganor E, Berger V, Garty L, Wietzen T, et al. Emergency room visits of asthmatic children, relation to air pollution, weather, and airborne allergens. *Ann Allergy Asthma Immunol* 1998;**81**(6):563-570.

28. Weber R. Cross-reactivity of pollen allergens: impact on allergen immunotherapy. *Ann Allergy Asthma Immunol* 2007;**99**(3):203-212.

29. Akinbami L, Moorman J, Liu X. Asthma prevalence, health care use, and mortality: United States, 2005–2009. National health statistics reports. Hyattsville, MD: National Center for Health Statistics 2011.

30. Cave AJ, Atkinson LL. Asthma in preschool children: a review of the diagnostic challenges. *JABFM* 2014;**27**(4):538.

31. Rabe KF, Adachi M, Lai CKW, Soriano JB, Vermeire PA, Weiss KB, et al. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *J Allergy Clin Immunol* 2004;**114**(1):40-47.

Figure 1. PRISMA flow diagram showing the progress of studies through the review

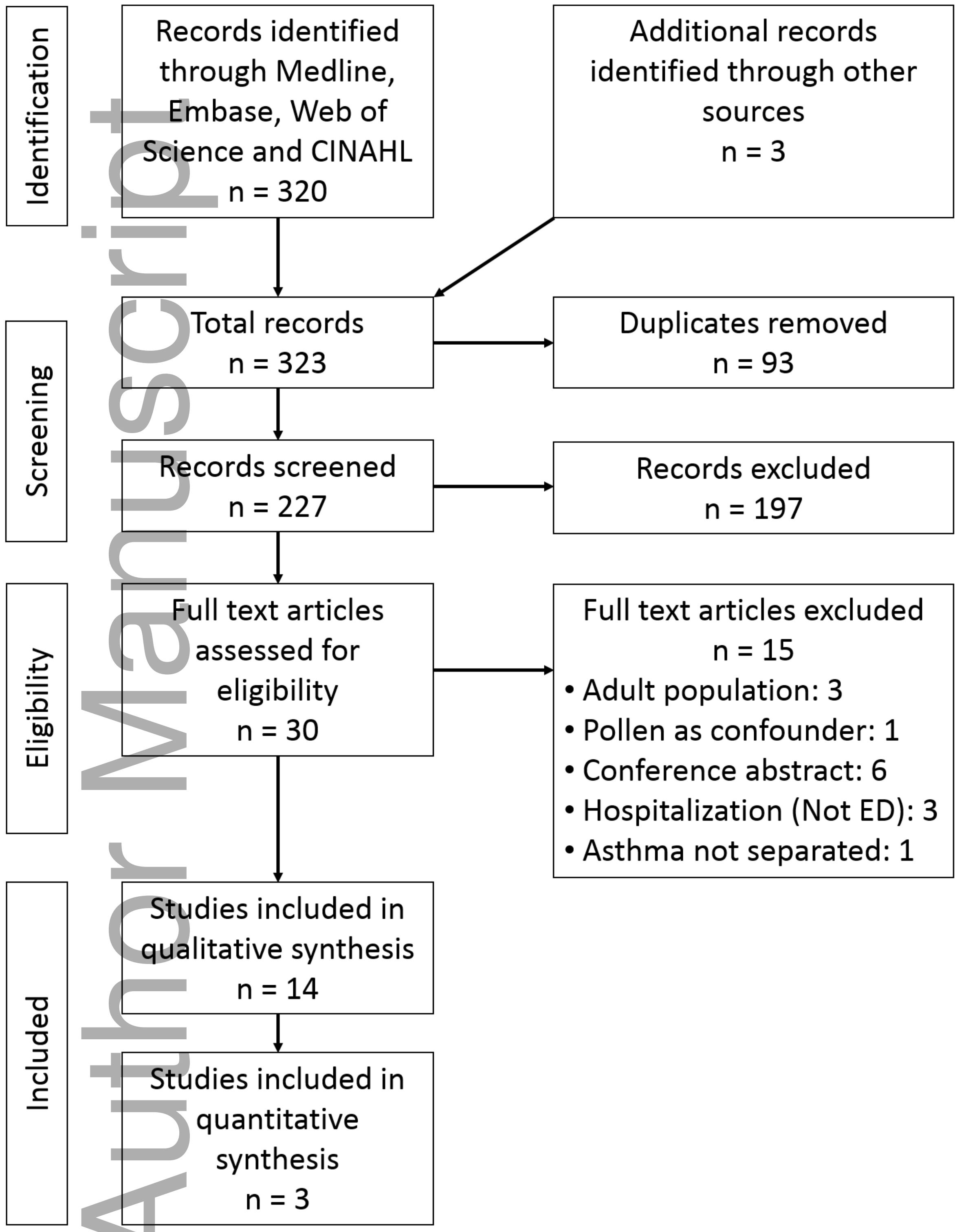


Figure 2. Associations between an increase of 10 grains/m3 of grass pollen and Mean Percent Change (MPC) of ED presentations in children and adolescents pooled using a random-effects meta-analysis.

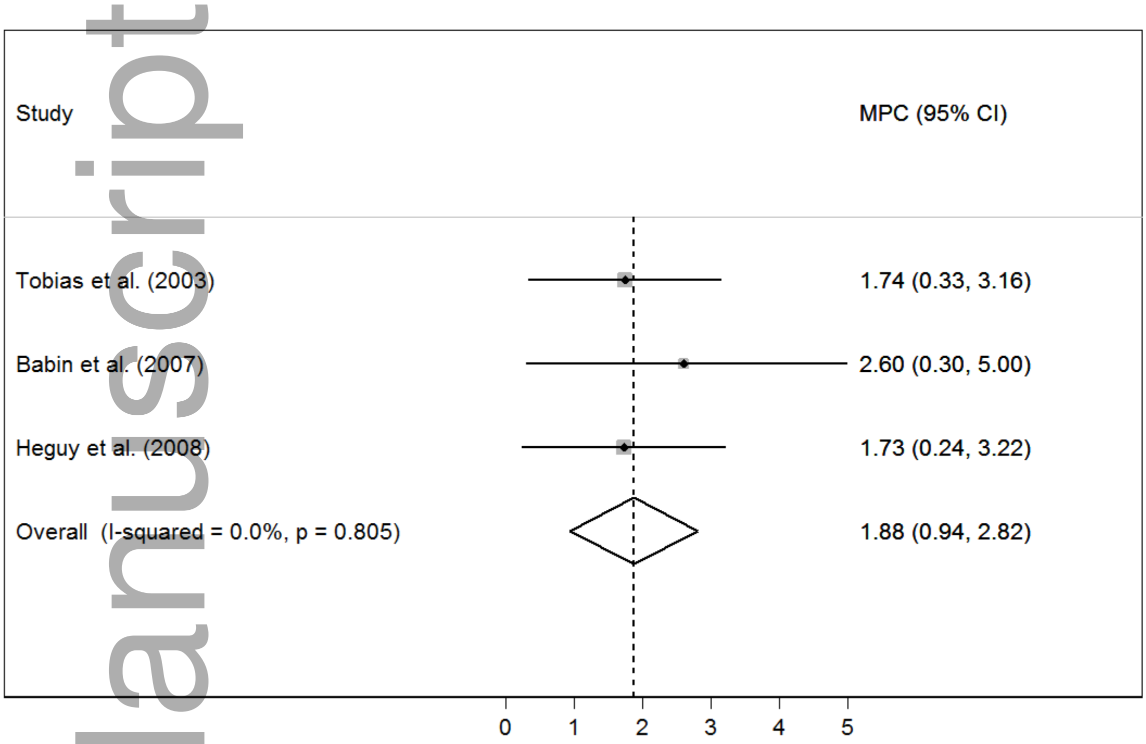


Table 1: Characteristics of included studies

Author (date)	Study Design and Method of analysis	Location	Time period	Method of pollen collection	Age group	Sample size
Ito (2015)	Time series	USA NYC	March-June 2002-2012	Burkard	0-4 5-17	~48,450* ~65,484*
Gleason (2014)	Time- series Case-Crossover	USA New Jersey	April-September 2004-2007	Not stated	3-17	21,854
Jariwala (2014)	Correlational study	USA NYC	2001-2008	Burkard	Not stated	22,717
Erbas (2012)	Time series – GAM[1]	Australia Melbourne	Sept-Dec 2003	Burkard	0-15	2,559
Darrow (2012)	Time- series Case-Crossover	USA Atlanta	1993-2004	Rotorod	0-18	199,533
Hayden (2011)	Descriptive epidemiological	Australia NSW	Jul1996-Dec 2009	None	0-15	9,495
Jariwala (2011)	Correlational study	USA NYC	Complete year 1999	Burkard	0-18	Not stated
Heguy (2008)	Time series	Canada Montreal	1994-2004	Rotorod	0-9	22,756
Babin (2007)	Time series	USA Washington, DC	Oct 2001-Sep 2004	Not stated	1-17 (5-12)	Not stated
Wang (2007)	Observational Retrospective	USA Pennsylvania	Jan 2000-Dec 2003	Not stated	not stated	1,460
Tobias (2004)	Time series – GAM[1]	Spain Madrid	1995-1998	Burkard	0-14	2,400
Lierl (2003)	Time-series- GEE[2]	USA Ohio	1996-1997	Rotorod	Not stated	~30,000*
Tobias (2003)	Time series – GAM[1]	Spain Madrid	1995-1998	Burkard	0-14	~2,400*
Garty(1998)	Correlational study	Israel Tel Aviv	Complete year 1993	Rotorod	1-18	1,076

*sample sizes are reported as an estimate of daily ED attendance.

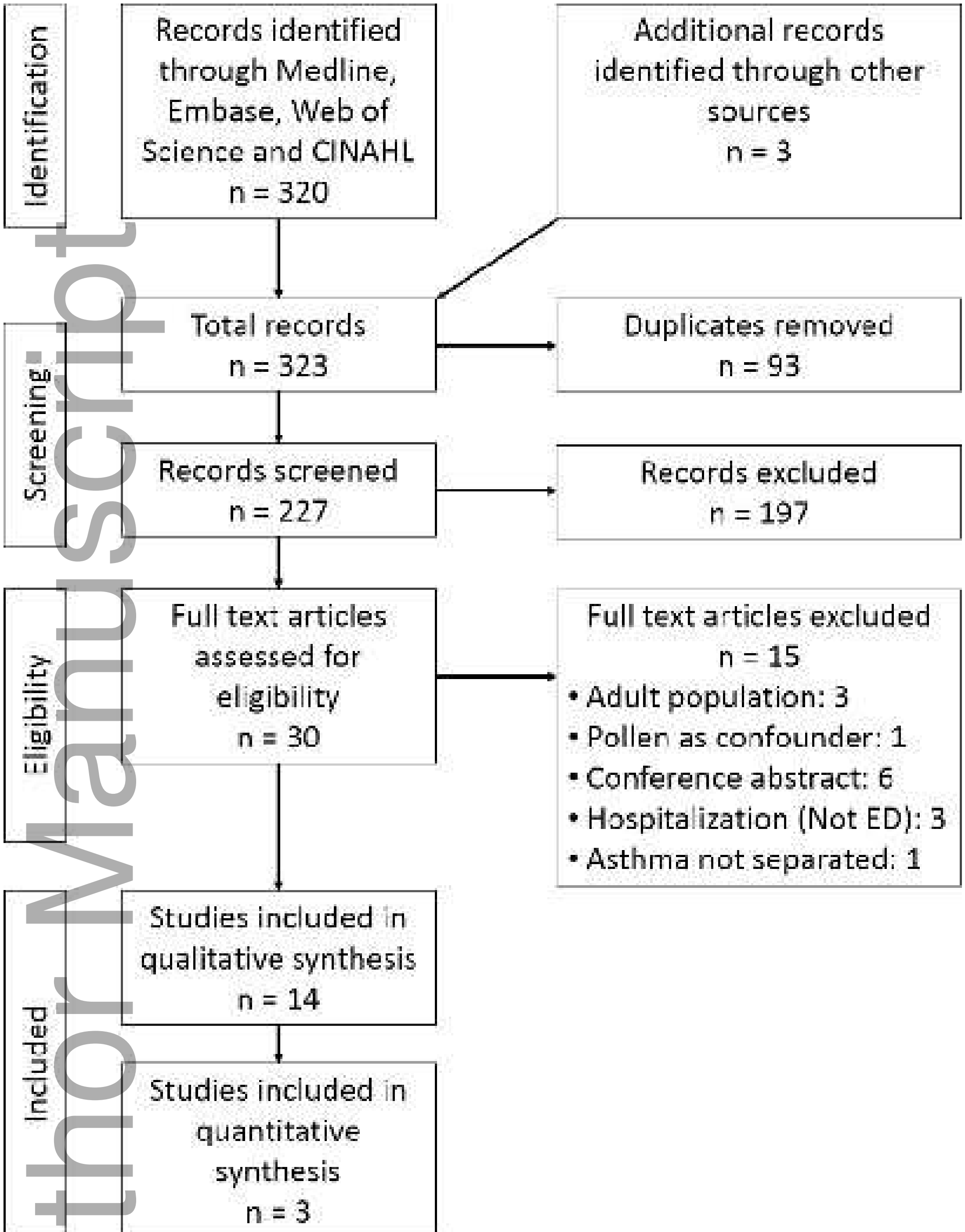
[1] Generalized Additive Models, [2] Generalized Estimating Equations,

Table 2: Definitions of outcome, exposure and summary of findings from each study included in the review

Author(date)	Exposure – pollen species	Outcome	Findings - including common names for pollen species	Confounders/ adjustments
Ito (2015)	Maple, birch, oak, elm, ash, sycamore, beech, hickory and poplar	"asthma", "wheezing", "COPD", common misspelled analogues and ICD-9 codes associated with asthma	Age dependent associations with asthma syndrome ED visits were found with the 5-17 age group showing the strongest association for maple, birch, oak, ash, sycamore, beech and hickory. Elm and poplar were not associated with asthma syndrome ED visits at any age group.	None
Gleason (2014)	Tree, grass, weed and ragweed	Asthma (ICD-9: 493.xx)	Tree and weed pollen were significantly associated with ED presentation at all lags examined with the highest relative risk seen across a five-day average (OR=1.23, 95%CI 1.21–1.25) and (OR=1.13, 95%CI 1.12–1.14), respectively. This relationship held true when a binary cut-off was used (OR=1.61, 95%CI 1.52–1.71 and OR=1.94, 95%CI 1.79–2.12, respectively). For ragweed, a negative association with paediatric visits was observed for all lag periods (OR=0.94 95%CI 0.94-0.95 for five day average). Grass pollen showed a significant increase in the risk of ED presentations for the five day average only (OR=1.02, 95%CI = 1.01-1.03).	3-day moving average temperature, 3-day moving average humidity, holiday indicator and school-in-session indicator
Jariwala (2014)	Grasses, trees and weed	Asthma (ICD-9: 493)	Tree pollen counts significantly correlated with paediatric asthma related ED visits (rho=0.33, p<0.001). No correlation between grass or weed pollen counts and paediatric asthma related ED visits.	None
Erbas (2012)	Grasses	Asthma (ICD10-AM)*,J45 J46	Strong dose-response association between grasses below 20 and childhood asthma ED presentations.	Day of week, time trend, temp, relative humidity, API, NO_2 and O_3
Darrow (2012)	Grasses, trees, weed and conifer	Asthma (ICD-9** :493.0-493.9)	Overall positive associations were observed with: grasses RR= 1.022, 95%CI: 1.012, 1.033 and Trees (birch RR = 1.022, 95%CI:1.013, 1.032 and oak RR= 1.028, 95%CI: 1.021,1.035)) Overall significant associations were observed for 5 to 17 year olds with trees RR=1.046, 95%CI: 1.033, 1.059 and Conifers RR=1.007, 95%CI: 1.001,1.013	3-day moving average of O3, CO, NO2, SO2, PM10 and PM2.5
Hayden (2011)	Grasses: Rye grass	Asthma (ICD-9 493 and ICD-10***) J45 and J46	Although actual pollen values were not modelled with ED presentations, the authors reported approximately 16% of children aged 5 to 14 years presenting to emergency with asthma during the peak pollen count days during the pollen season.	None
Jariwala (2011)	Trees and weeds: Tree pollen	Asthma (ICD-9: 493)	Peak asthma ED visits (peak asthma ED visits were identified as the number of visits that exceeded the 99.9% confidence intervals for the identified time interval n~ 35 for children) occurred during spring with high tree pollen counts correlation coefficient 0.9 p = 0.03	None
Heguy (2008)	Grasses, trees and weeds	Asthma (ICD-9: 493)	Mean Percentage Change (MPC): For grasses at lag 3 days:1.73, 95%CI:0.24,3.25; lag 5 days:1.43, 95% CI: - 0.06, 2.95 For weed at lag 2 days:-0.54, 95% CI:-0.93,-0.15 and lag 3 days -0.66, 95% CI:-1.07 to -0.25.	Daily maximal concentrations of NO2 and O3. Daily minimum and maximum temperature, maximum air pressure and change in air pressure from previous day.

Babin (2007)	Grasses, trees and weeds	Asthma (ICD-9: 493)	MPC: 1-17years Grasses (10 grains/m^3): lag 0: 0.7 (-1.8, 3.1); lag 1: 1.9 (-0.4, 4.3); lag 2: 2.3 (-0.1, 4.7); lag 3: 2.6 (0.3, 5); lag 4: -0.4 (-2.9, 2.3) Tree (100 grains/m^3): lag 0: 0.5 (0, 1.1); lag 1: 0.4 (-0.2, 1); lag 2: 0.5 (-0.1, 1.1); lag 3: 0.2 (-0.4, 0.8) MPC: 5-12years Grasses (10 grains/m^3): lag 0: 1.6 (-2, 5.4); lag 1: 3.5 (0.1, 7.1); lag 2: 4.3 (0.9, 7.9); lag 3: 5.5 (2.2, 9); lag 4: 3.1 (-0.5, 6.8) Tree (100 grains/m^3): lag 0: 1.8 (0.9, 2.6); lag 1: 1.2 (0.4, 2.1); lag 2: 1.5 (0.7, 2.4); lag 31.1 (0.3, 2); lag 4: 1.1 (0.2, 2) Weed (10 grains/m^3): lag 0: -2.9 (-6.8, 1.1)	Ozone, PM2.5, mold spore counts.
Wang (2007)	Grasses, trees and weeds	Asthma (ICD-9: 493)	Tree and weed pollen trended higher on days with ≥ seven asthma-related ED visits (p=0.05), but there was no significant difference in grass pollen between high- and low-visit days.	None
Tobias (2004)	Grasses, trees and weeds	Asthma (ICD-9: 493)	Increase in risk for ED presentations was 31.3% to 78.9% for grasses 49.8% for trees	Daily averages of NO2, SO2, PM10, temp and humidity. 8 hour maximum O3.
Lierl and Hornung (2003)	Grasses, trees and weeds	Asthma (ICD-9: 493)	log of pollen counts lagged 3 days was the most significant predictor: rate ratio (RR):1.089, (95% CI: 1.027-1.155) in a model with month of the year **Pollen counts** and **season** interaction: ln (pollen) spring &summer: RR: 1.145, 95% CI:1.076,1.217	None
Tobias (2003)	Grasses, trees and weeds, conifers	Asthma (ICD-9: 493)	MPC of ED presentations associated with a $95-99^{th}$ percentiles increase in different types of pollen levels: Olive lag 1: (1.8 ,95% CI: -7.9,12.5) Grass lag 2: (15.9,95% CI: 6.5,26.2) Grasses lag3: (17.1 , 95% CI: 3.2,32.8) Nettles lag1: (8.4 ,95% CI: 2.8,14.4), Mugwort lag1: (4.4,95% CI :-6.6,16.7) Cypress lag3: (6.0, 95%CI :-3.4,16.5)	Daily averages of NO2, SO2 and PM10. 8 hour maximum O3. Mean daily temperature, mean relative humidity.
Garty (1998)	Grasses, trees and weeds, conifers.	doctor diagnosed asthma	No significant correlation was observed between the airborne pollen concentration peaks and asthma ED visits peaks.	None

ICD-10AM: International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (1999-present) – codes J45, J46
** ICD-9: International Classification of Diseases, Ninth Revision (1979-1998) – codes 493
***ICD-10: International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (1999-present) – codes J45, J46
ICD-International Classification of Diseases, a global health information standard for mortality and morbidity statistics.
ICD-9-CM-The International Classification of Diseases, 9th Revision, Clinical Modification
-ICD-10-AM refers to the Australian modification of the WHO ICD-10 base classification system. Its proper name is the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification. This version of ICD has been modified to serve particular Australian needs and to support the national collection of data relevant to our population's health.



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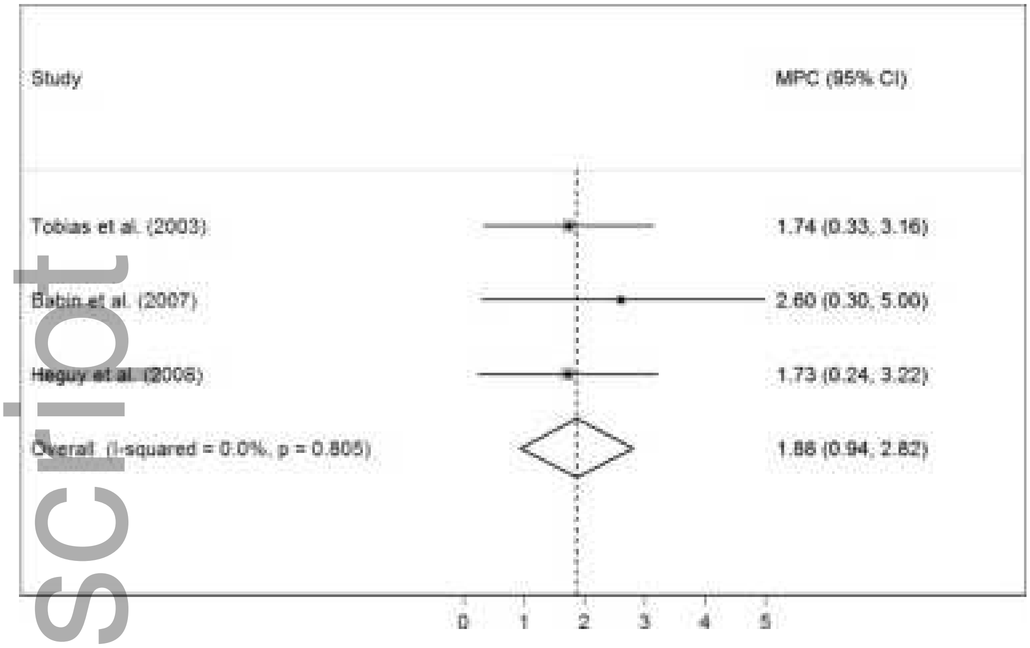

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